The Nature and Function of the Alpha Cells of the Pancreas

Their Possible Role in the Production of Glucagon

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During the past few years attention has been focused on the alpha cells of the pancreas and on the protein known as glucagon or hyperglycemic-glycogenolytic factor of the pancreas (HGF). The literature on glucagon has recently been reviewed in detail by various authors.[1-5] That on the alpha cells has been touched on only briefly in the majority of papers, with the exception of a review article by Volk, Lazarus, and Goldner.[6] Because the literature is so extensive and the subject controversial, it is believed that a thorough and critical appraisal of available data on the alpha cells, particularly as to a possible relationship to glucagon, is indicated. In the present paper such a review is presented in the light of hitherto unpublished results of experimental work carried out in this laboratory during the past year.

THE ALPHA CELLS OF THE PANCREAS

Although observations that the islets of Langerhans contain more than one type of cell date back to 1899,[7] the first adequate distinction between the cell types was accomplished in 1907 by Lane,[8] who observed that some of the cells in guinea pig islets contained granules which dissolved in alcohol, whereas the granules in other cells were insoluble. He designated the latter as alpha cells and the former as beta cells.

Staining methods

In the half-century since Lane's discovery, various methods of specific staining of islet cells have been designed. The term "specific" is applied here in the sense of selective demonstration of the cell types within the islets or within the pancreas. It cannot be applied in the sense of staining only alpha cell granules, since it is known that many other cell types, granules, or tissue elements outside the pancreas stain rather nonspecifically with many of these staining methods. Unfortunately, there has been a tendency in certain recent papers to conclude that some extrapancreatic cells stained with these procedures were identical with islet cells, a conclusion which is not justified.

All staining methods for islet cells (with the exception of some silver methods) require immediate and proper fixation of the tissue if they are to be successful, since the islet cell granules are very easily dissolved if improper fixatives are used or if the time between death and fixation is too long.[9] This sometimes makes their application to human material extremely difficult. Results in animal material, where this drawback need not exist, are usually much better, but excellent staining results are not yet obtained in all species. There is hope, however, that good results may be obtained in all species with the choice of the right fixative and slight modifications of staining procedures.[10]

A satisfactory method for staining islet cells should be a simple procedure which provides selective staining as well as good color contrast between the various cell types in the islets and between these cell types and the exocrine tissue elements. If possible, the staining procedure should be relatively independent of a need for fresh tissue and thus become of greater value in work with human material. From the following brief discussion of staining methods now in use it will be seen that there does not exist a method which fulfills these requirements.

The so-called "neutral stains" developed by Lane[8] and Bensley[11] were in use between 1907 and 1931. The use of these stains resulted in the discovery in the guinea pig of a third cell type, the C cell. Unfortunately, the neutral stains are not entirely adequate when

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used with the pancreas from species other than the guinea pig, and as a result much confusion has arisen. Subsequently the introduction of the Mallory-Heidenhain Azan stain led to the discovery of a fourth cell type, the D cell.[12] Although this stain easily differentiated alpha granules from granules of the D cells (red and blue), it was far from satisfactory, since the alpha granules were not well contrasted with the yellowish-orange granules of the beta cells. Furthermore, the faint staining of beta granules made it almost impossible to evaluate degranulation processes in these important cells.

Since 1939 Gomori[13–17] has made the greatest contributions to the staining of islet cells. The first procedure developed was a chromium-hematoxylin stain in connection with phloxine or ponceau de xylidine.[14, 15] This method has been modified and apparently improved by Nerenberg.[15a] The second was the aldehyde-fuchsin stain,[16] which has even more advantages than the first, especially when combined with Gomori's modification of Masson's trichrome stain.[17] With these methods, particularly the latter, the beta cell component of the islets is well brought out; the beta granules give an excellent contrast to all other islet cells since they are stained deep purple.

The use of phloxine or ponceau de xylidine does not aid in differentiating alpha from D cells, since both are stained red. With the modification of the trichrome stain this differentiation seems possible, since the former cells stain pink and the latter are said to stain green. However, use of either of the staining procedures sometimes brings difficulties in differentiating the alpha cells in some animals (rat, hamster, etc.), although it gives excellent results in guinea pigs.

Although Gomori's granule stains allow the simultaneous demonstration of all known cell types of the islets, the technics are difficult and are applied best to freshly fixed material. Therefore, still in use are several other methods which do not stain simultaneously all of the cell types. Thus a number of silver impregnation technics (the so-called silver stains) are common procedures; however, it is necessary to distinguish between two groups of reactions with silver, that shown by the "argentaffin" and that by the "argyrophil" cells or substances.[18–25] Although these terms have the same literal meaning, they are used in practice to differentiate two types of substances. Those in the first group (argentaffin) have in themselves the property of directly reducing ammoniacal silver solutions (Masson-Fontana technic), whereas those in the second (argyrophil) require an added reducer, applied before or after the silver solution. The argyrophil reaction is nonspecific but can be used conveniently to delineate a fairly well defined group of cells in various parts of the body besides those in the islets of Langerhans.[18]

The two most popular methods of applying this reaction are the Gros-Schultze method on formalin-fixed frozen sections as introduced for the demonstration of alpha cells by Ferner,[25] and more recently the Bodian method in paraffin sections of tissue fixed in either Bouin's fluid or in Bodian's alcoholic solution.[26] The Gros-Schultze method and its modifications[25, 27–29] have been in extensive use in Europe, since they give good results even in material fixed several hours after death. Silver-positive cells give a very good contrast with unimpregnated islet and acinar cells. Since it is now believed that with this method not all of the alpha cells are impregnated and that possibly some of the beta cells may be demonstrated,[30–33] Bodian's method seems to have become increasingly popular. In addition this method is not as capricious as the Gros-Schultze method.

There are various other methods for the demonstration of alpha cells, but only a few may be mentioned here. Hultquist and Tegner's modification of Mallory's phosphotungstic acid-hematoxylin stain[34] and Mann's eosin-methyl blue mixture have been used recently.[35] For details of various staining methods the reader is referred to the chapter on staining methods in the monograph by Warren and LeCompte.[36]

Comparing the relative values of the various methods, one gets the impression that the modern granule stains are superior methods which appear to differentiate the alpha component of the islets. The simultaneous staining of all known cell types in the islets is of extreme value in modern islet cell research, even if these methods are far from being completely satisfactory in all species. The granule stains are highly reliable for the identification of these cell types as long as the specific granulation of the cells is present. If this is not the case, as in cells with mitotic activity or in completely degranulated cells, the identification of a cell type becomes either extremely difficult or impossible. In these instances it seems much better to introduce the term "unclassified cell" than to attempt a classification based on doubtful differences.

Cytology

The nuclei of normal alpha cells do not differ greatly from those of beta cells, although they are said to be poorer in chromatin than are the latter in most species.[37] The only animal in which a distinction of

the cell types may be accomplished by their nuclear differences alone seems to be the normal guinea pig. Alpha cells may be found in all variations of size and shape, although generally they are said to be larger than beta cells. The shape of the alpha cell has been compared with that of the flame of a burning candle.[15] With silver methods alone, ramifications of protoplasm from the alpha cells and reaching between the surrounding cells are reported.[38] There is no general agreement as to the normal size of alpha granules; this may be due to differences in methods. Sometimes the granules are so numerous that it becomes difficult to distinguish one from the other, and sometimes granules are rare.[15, 38, 39]

Pattern of distribution

Alpha cells have a general tendency to nestle along capillaries.[15, 38] The general distribution of alpha cells in the islets differs in some species. Thus one is able to make the diagnosis of the species with some certainty from the islet pattern alone. Alpha cells are more or less scattered all over the islets in man, dog, bat, and guinea pig, and appear in the guinea pig in clusters.[15, 37, 38] They are found in the periphery in the rabbit, opossum, mouse, rat, and hamster, and in the last three animals there are thought to be more or less complete layers of cells surrounding the central bulk of the beta cells.[15, 37, 38] A more central position as well as a peripheral one is reported in the cat and the horse;[15] however, there is not complete agreement that the central cells in the horse are really alpha cells.[27, 31, 38] An interesting arrangement of the cell types occurs in birds. Here the two main types of islet cells seem to form different islets, the so-called light islets and the dark islets. Whereas the former are reported to consist mainly of beta cells, the latter are said to consist predominantly of alpha cells and D cells.[40, 41] Recently vanCampenhout and Cornelis made the statement (cited by Vuylsteke and deDuve[42]) that "the pancreas of birds is particularly rich in a type of cells resembling alpha cells in all their staining properties, except that they show a low argentaffinity."

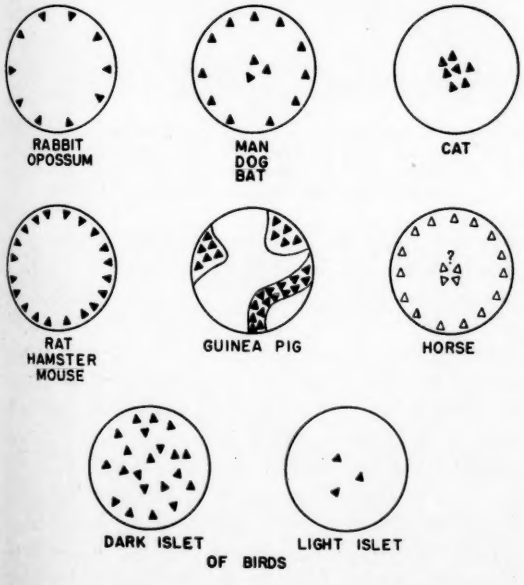


FIG. 1. Diagrammatic representation of species variations in arrangement of alpha cells in islands of Langerhans.

It may be seen from these few examples that the cellular pattern in the islets of various animals sometimes differs considerably from the cellular pattern in man. The reason for this behavior is not yet known, but these species differences serve as an illustration of the care which must be used in applying conclusions to man from experimental data obtained in animals.

With the introduction of more satisfactory staining methods, attempts have been made to get an insight into the quantitative as well as the qualitative cellular composition of the islets. It is impossible under present circumstances to estimate the absolute number of alpha cells in a whole pancreas and difficult to do so even in a single islet. Such actual counts need painstaking methods and above all great patience. Ogilvie[43] of Edinburgh is at present working on such a project.

In the meantime we know only that in nondiabetic individuals and most animals the number of beta cells is much higher than that of the alpha cells and the latter considerably higher than the number of D cells. For practical purposes it has become customary to express the relative number of alpha and beta cells in either a percentage or in an alpha to beta ratio or index.

Figures reported in nondiabetic humans and normal animals are listed in table 1.

One sees at a glance that the figures obtained by various authors differ considerably. These differences may be explained by the relatively small number of individuals counted in each species and perhaps by the relatively small number of islet cells counted by some authors. There is not yet general agreement as to the minimum number of cells which must be counted to get statistically significant data. Furthermore, some of these counts have been done with different staining methods and particularly the Gros-Schultze method, with its dependence on relatively thick frozen sections

TABLE 1

Percentage of alpha cells in total cells of the pancreas in normal man or animals

Author	Species	Alpha cells (per cent)
Ferner[38, 44-46]	Human	20
Hess[47]	Human	10
Terbrüggen[48]	Human	25
Gomori[15]	Human	10-40
Hultquist and others[29]	Human	33-35
Creutzfeldt[33]	Human	9-68
V. Rehren[38]	Guinea pig	19.9
Johnson[49]	Guinea pig	20.7-22.2
Grobety[35]	Rat	18
Ferner[38]	Rat	23
Hultquist and others[29]	Rat	5.3-10.7
Ferner[38]	Rabbit	About 20
Hunt[50]	Dog	20
Ferner[38]	Dog	20
Creutzfeldt[51]	Dog	12

and lack of differentiation between alpha cells and D cells. Gomori,[15] who noted very wide fluctuations of the normal range in nondiabetic humans even with modern granule stains, doubts very much the actual value of these counts.

Embryology

The application of modern staining methods to pancreases of human and animal embryos and the recent attempt to evaluate qualitative and quantitative differences of the islet pattern in various stages of prenatal development have brought about some interesting details hitherto overlooked. Papers on this subject are still few, and so far as animal material is concerned rather contradictory. Thus, Hard reports that the first alpha cells differentiate in the rat[52] on the second postnatal day, whereas in the guinea pig,[53] with a much longer gestation period, the first alpha cells differentiate much earlier.

In human embryos the first occurrence of alpha cells is not yet known. Ferner, in one of his earlier papers,[25] was of the opinion that the first differentiation of alpha cells takes place before the differentiation of beta cells. In this early investigation he worked with silver methods and thought that all silver cells, which he found to be identical with the "trueben Zellen" of Neubert, were alpha cells. He expressed the belief that these silver cells were forerunners of beta cells and called them therefore unripe or "inselpotente" cells. When, with the aid of modern granule stains, it became apparent that the primitive anlage of islets does not consist of alpha cells alone but also of beta cells, Ferner had to revise this view.[54] It is now assumed that both cell types develop independently from undifferentiated duct or primitive tubule cells. When this differentiation occurs is not yet known.

With the aid of silver stains[25] and later on with granule stains[54] it has been shown that the embryonic cellular pattern of the islet differs quite remarkably from the cellular pattern in human adults. In early stages buds come out from primitive ducts or tubules which grow toward a center (Neubert's "islet field"), thus forming a primitive islet. In these primitive buds and islets a peculiar arrangement of the cell types may be observed which becomes even more marked in the so-called "mantle islets." These mantle islets prevail in the period from the fourth embryonic month until the end of the pregnancy and are characterized by a peripheral layer of alpha cells surrounding the central bulk of beta cells. Ferner and Stockenius[54] observed a zone of ungranulated cells between alpha and beta

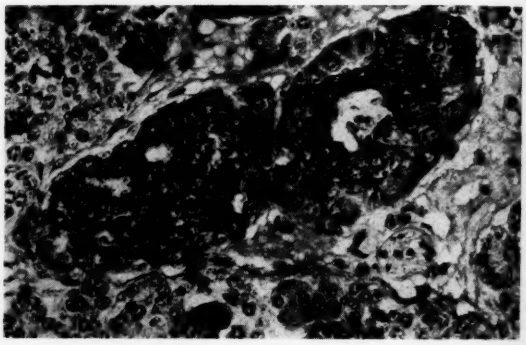


FIG. 2. "Mantle islets" in pancreas of guinea pig embryo. The central mass of beta cells (black in photograph) is surrounded by a layer of alpha cells (grey in photograph). Gomori's aldehyde-fuchsin and trichrome.

cells and think that this may represent a transition between alpha and beta cells. They came to this conclusion from the observation of a great number of mitotic figures in the alpha cell area, the absence of mitotic activity in the beta cell area, and the appearance of these transition cells whose nuclei they believe to resemble beta cell nuclei. The last point does not seem of great value since it is in contradiction to the general belief and, indeed, to Ferner's own statement that in man there is no way to differentiate islet cells by nuclear characteristics.[38] Schultze-Jena[55] was able to identify mantle islets in human embryos during later embryonic life but failed to find the typical transition zone as described by Ferner and Stockenius. In his slides undifferentiated cells were scattered over the

islets. Whether or not these undifferentiated cells are real transition cells is hard to decide. They are certainly not if one applies Gomori's criteria of a transition cell.[15] According to this author a transition cell should contain both alpha and beta granules. Valuable as this criterion is as warning not to interpret artefacts due to poor staining technic as histologic facts, it should be pointed out that this need not necessarily be the only form of a transition cell.

Alpha cells develop according to Ferner[38] during embryonic life in two different ways: by differentiation from undifferentiated exocrine epithelium (primitive ducts and tubules) and by cell division from alpha cells themselves. Interestingly enough, there is a relative abundance of alpha cells during late embryonic life, and at this time they are about equal in number with the beta cells. During the first postnatal years the relative number of alpha cells gradually decreases until the usual numeric pattern of the adult islets develops. The fate of the alpha cell is unknown. In adult islets, at least, transitions from alpha cells into beta cells do not seem to occur; however, transitions into D cells have been reported.[15]

The influence of various experimental procedures on the alpha cells

In contrast to the abundant literature on the effect of various experiments on beta cells, systematic investigations on the influence of experimental procedures on alpha cells have been few. Most of these investigations need confirmation with modern granule stains.

The influence of diet on alpha cells has been reported by several authors; however, these studies were done mostly from the standpoint of general changes in the islets and particularly in beta cells. An increase in number of alpha cells has been reported during starvation;[44, 56-59] however, the contrary has also been found.[60] It is hard to evaluate how far degranulated beta cells have been confounded with alpha cells in these papers, but this possibility must be kept in mind, particularly in the older work. Sergeyeva[61] reported a great increase of alpha cells several hours after the feeding of cream to cats. No such changes occurred when modern granule stains were applied to the guinea pig after the feeding of cream by stomach tube.[62] It is now generally agreed that dextrose administration causes changes in beta cells but leaves alpha cells intact. Likewise following the administration of alloxan, changes in alpha cells, if any, are only slight and apparently without pathologic significance for the development and the severity of alloxan diabetes. A single paper which reports alpha cell damage as well as beta cell damage after alloxan[63] is open to criticism, since this observation was based on observations in living animals, in which cell differentiation is hard to obtain.

After prolonged administration of insulin, degranulation and decrease in number of alpha cells have been reported,[41, 60] although others[25, 57, 64] have found an increase in number. An increase in alpha cells in the pancreas of patients with functioning islet (beta cell) tumors has been reported.[48, 65]

An apparent influence of epinephrine and the sympathico-adrenal system on alpha cells was found by Sergeyeva.[61, 66] Alpha cells were said to increase in number after stimulation of the splanchnic nerves in cats or epinephrine administration but to decrease after adrenalectomy and blocking of the sympathetic nervous system.

Anterior pituitary extracts and growth hormone have been thought until recently to exert an effect on beta cells only. The relative increase of alpha cells which predominated in the islets when beta cells were damaged by anterior pituitary extracts[67-69] was believed not to play an active role in the development of metahypophyseal diabetes. Ferner[46] and Ferner and Tonutti,[70] however, observed a decrease in the number of alpha cells after hypophysectomy in rats and guinea pigs, which caused Ferner[46] to speak of an "alphacytotropic factor of the anterior pituitary." Although growth hormone is said to increase the mitotic activity of alpha cells in rats,[71] others have not noted any influence on alpha cells after hypophysectomy or growth hormone injection.[72, 73] Volk and Goldner[74] found no change in the islets in hypophysectomized rats surviving up to four and a half months, but the administration of large doses of purified growth hormone to hypophysectomized rats led to an absolute and relative decrease of alpha cells, with degranulation of surviving alpha cells and of beta cells. Corticotropin[71] and cortisone[75, 76] although they stimulate the beta cells do not seem to exert any stimulating effect on the alpha cells.[71, 75, 76]

Theories on the supposed function of alpha cells and their historical background

Up to the 1940's the only cell type in the islets actively connected with carbohydrate metabolism was considered to be the insulin-producing beta cell. Indeed, even today many aberrations of carbohydrate metabolism are explained by pathologists on the basis of damage or destruction of this important cell type. So the general conception that alpha cells might be an inactive type of islet cells prevailed.[25, 48, 57, 77]

A more active role of the alpha cells in carbohydrate metabolism was suggested, however, by Ferner[44] when

he began to study the alpha to beta ratio in the pancreases of diabetics. He reported that in every diabetic a shift of the normal ratio toward the alpha side was a common finding, and was even of the opinion that this shift was pathognomonic for diabetes. The relative increase in the number of alpha cells in the diabetic islets had some resemblance to the situation which this author encountered during certain stages of the development of islets in human embryos, in which there is prevalence of alpha cells in the late embryonic period (see above). This led him to the hypothesis that alpha cells may be immature islet cells, with potency to form beta cells, and thus that diabetes could be interpreted simply as an example of maturation arrest of these alpha cells. The validity of both the pathognomonic significance of the shift of the alpha to beta ratio and the hypothesis of the maturation arrest of alpha cells in diabetes has been open to criticism.

Although Hess[47] supported Ferner's findings without reservation, the diagnostic or even pathognomonic value became doubtful when later investigations carried on with the same silver methods as employed originally by Ferner or with Gomori's granule stains revealed some overlapping between the alpha to beta ratio of nondiabetic and diabetic pancreases.[15, 48] In Creutzfeldt's[33] material many diabetics had a normal alpha to beta ratio, whereas many nondiabetics showed the increased ratio of silver cells which Ferner believed to be pathognomonic for diabetes. Gomori[78] with the aid of granule stains detected normal ratios of islet cells in as many as 60 per cent of patients with clinically unquestionable diabetes.

The hypothesis of Ferner that alpha cells are immature islet cells and that diabetes is explainable by a maturation arrest has been challenged also by Terbrüggen.[48] He points out that if this were true, one should find many more alpha cells in islet cell adenomas, according to the general rule that tumors consist to a high degree of immature elements. This is, however, not the case. The situation in alloxan diabetes similarly speaks against this hypothesis. Terbrüggen came to the conclusion that alpha cells either are inactive islet cells or have another function.

The concept of endocrine activity of the alpha cells was not completely new. The observation of granules in these cells and their location in such endocrine structures as the islets of Langerhans had already led earlier investigators to the belief that these cells may be engaged in an endocrine activity.

For a short period the possibility was emphasized that alpha cells might secrete "lipocaic,"[79, 80] a hypothetical fat-metabolizing hormone. The occasional coincidence of degenerated alpha cells with fatty degeneration of the liver, however,[69, 81] seemed to support this view. But since it now is doubted that the lipotropic activity of the pancreas is endocrine in nature,[82] it does not seem justifiable to maintain this hypothesis.

In recent years, it has become more and more customary to link the alpha cells with the production of a second endocrine factor of the pancreas, which could have an effect on carbohydrate metabolism different from insulin. The hypothesis that there exists such a factor, presumably a hormone, which would clarify hitherto unexplainable findings was derived from three different fields of experimental and clinical work.

The first one was the clinical observation that, following total pancreatectomy, diabetic patients did not require more insulin than they did before operation, but sometimes even considerably less (about 40 units a day). It was concluded that this was evidence for a pancreatic anti-insulin factor which might be responsible for the high insulin requirement of some diabetic patients and some forms of insulin insensitivity.[83-89]

The second argument in favor of another endocrine pancreatic factor came from experimental work with alloxan-diabetic animals.[90-93] It has been demonstrated that after total or subtotal pancreatectomy in these animals the total insulin requirement drops significantly and rapid development of ketosis and coma occurs. Here again an anti-insulin factor capable of raising the blood sugar and preventing ketosis has been hypothesized, although according to experimental work by Mirsky and his associates,[94] differences in the insulin sensitivity of animals before and after pancreatectomy may be explained in another way.

The third and perhaps the most important support came from biochemical research when a pancreatic factor with hyperglycemic and glycogenolytic properties, previously known as glucagon, again awakened the attention of biochemists.

It is not surprising that the production of such a factor was linked with the alpha cells. Heard and his collaborators, as far as can be determined, were the first to do this when they referred to this factor as "an alpha cell hormone of the pancreas."[95] This statement was accepted without question by many clinicians and experimental workers. However, one wonders if it were not made a little too hastily, since in recent years some doubt has been expressed as to whether all experiments which at first seemed to support this belief actually did so.

ALPHA CELLS AND GLUCAGON

Before starting a discussion on the still controversial subject of alpha cells and glucagon it may be of value to summarize briefly our knowledge about the latter substance.

Chemistry

First observations on glucagon began when several authors[96-98] noted that the first, still rather crude insulin preparations injected intravenously caused a small, transient initial rise of the blood sugar curve before developing their hypoglycemic activity. Murlin gave the name "glucagon" to the substance which he believed to cause this effect. Bürger's group in Germany did a great deal of work on the problem of the primary hyperglycemia of certain insulin preparations (the "glucagon effect"). They even attempted the separation of glucagon from insulin.[99] Although they were able to inactivate insulin partially by treatment with alkali and cysteine and thus increase the hyperglycemic effect of the extract, they were not successful in making a separation. In 1949, Sutherland, Cori, Haynes, and Olsen,[100] using the formation of insoluble fibrils of insulin with hot hydrochloric acid, succeeded in obtaining separation of an impure glucagon preparation. The purest glucagon preparation to date seems to have been made by Staub, Sinn, and Behrens.[101]

Glucagon is an undialyzable polypeptide which gives various protein reactions and as a protein is broken down by proteolytic enzymes.[100-106] Electrophoretic studies have been done and determinations of the amino-acid content reported.[100, 107-109]

The chief sources of glucagon are various insulin preparations, although its separation from other materials has been claimed by various authors.[99-103, 105-111]

There are three assay methods for glucagon, the two more popular ones being based on the height and duration of the hyperglycemia when injected intravenously into test animals (usually rabbits) or the glycogenolytic action on test liver slices incubated in a proper buffer solution.[100, 102] A third assay method, not in general use, is based on the ability of glucagon to counteract large amounts of insulin.[1]

Physiologic role

The only effect of glucagon known for certain is its lytic action on liver glycogen, and this is dependent on an intact liver cell system. It seems to take place at the liver phosphorylase level.[100, 162] Glucagon does not appear to affect muscle glycogen, since in animals after hepatectomy or total evisceration no hyperglycemic response with this protein is obtained.[105, 112]

Besides this well established action on liver glycogen several other actions of glucagon have been reported.[1, 113] It is, however, not yet clear whether these actions are due to impurities of glucagon preparations or to side actions through the influence on liver glycogen.

The question of the physiologic or pathologic importance of glucagon is not yet settled. Several authors are of the opinion that it is a hormone,[3, 4, 95, 114] whereas others believe that its hormonal status is not yet proved.[1, 115, 116] A convincing example of a deficiency picture has not yet been established, either clinically or experimentally.[117] (See below.)

The diabetogenic action of glucagon is not yet agreed upon. There are several authors who present evidence that glucagon may exert such an influence by the following pathways:

(1) By an insulin-inhibiting effect, as concluded from observations on the isolated diaphragm[95, 118] or in hepatectomized and nephrectomized animals.[119]

(2) By an increased secretion of glucagon after growth hormone injections.[120, 121] It has even been suggested that glucagon itself may exert growth promoting activities. However, the observation of Elrick[122] that glucagon increases the width of the epiphyses in the hypophysectomized rat could not be confirmed with a pure glucagon preparation.[123]

(3) By the stimulation of the adrenal cortex by glucagon.[124]

(4) By synergistic action in combination with other diabetogenic hormones (growth hormone, corticotropin, and cortisone).[125]

However, Bürger,[99] one of the most distinguished students of this substance, holds that the physiologic action of glucagon is synergistic rather than antagonistic to insulin. He believes that glucagon prepares the necessary amount of glucose from the glycogen stores of the liver for the action of insulin.

Site of origin

One of the most discussed and still unsolved problems of glucagon is its site of origin. Bürger[99] has suggested that it may be produced in the pancreas, and the close connection with insulin which causes so much trouble in purification of this substance seems to support strongly this assumption. Further evidence for this view came from the observation of Sutherland and deDuve[110] that a substance apparently identical with glucagon was found in the pancreases of all species examined. The only question was which part of the pancreas, exocrine or endocrine, might be the source of this factor and, so far as this could be decided, which cell type.

Theoretically both endocrine and exocrine tissue could be the source, although of course the assumption that glucagon is a hormone would favor the islets of Langerhans as a possible source. The observation that a material presumed to be glucagon was found in a distribution in the pancreas which resembled roughly the distribution of the islets seemed to support this view.[110] However, these experiments, although suggesting the probable endocrine site of formation, are not entirely convincing.

There exists one animal species in which the question of whether glucagon is produced in the exocrine or endocrine part of the pancreas could be decided without too much effort. In teleosts there is a fairly good separation between islet tissue and exocrine parenchyma,[126, 127] and Audy and Kerly[111] reported that they were able to demonstrate with the liver slice method an appreciable amount of glycogenolytic material in the islet tissue of *Lophius piscatorius,* whereas only mineral amounts of it were found in the exocrine tissue. With this the question seemed settled. Unfortunately, these authors did not examine the hyperglycemic response of their substance in test animals. This might have been of value since Weitzel and associates,[128] who tested the primary hyperglycemia of insulin in ten teleost species, were not able to observe any and thus concluded that this indicated a lack of glucagon. This absence of a primary hyperglycemia (glucagon effect) of fish insulin was observed by others.[129, 130] It became apparent only when pancreatic extracts from fish were inactivated with alkali.[130] Weitzel,[128] however, doubts that the hyperglycemia following the injection of inactivated raw insulin extracts is actually due to glucagon, since he feels that it might be due to other substances which are split off from the insulin molecule during the process of alkali inactivation.

Another procedure used in an attempt to show the origin of glucagon was the use of ligation of the excretory duct. With atrophy of the exocrine tissue it would thus be possible to exclude this as a source of glucagon and to identify the endocrine origin of this substance. Indeed, it has been reported that these preparations seem to have roughly the same amount of a hyperglycemic substance as normal pancreas with the exocrine tissue intact.[110, 114, 118]

The decision of whether the beta cells or the alpha cells may be the cellular site of origin of glucagon had to be made, since it was not impossible that the latter actually could be the producers of this factor. Several authors[110, 114] tried to settle this problem with a slightly different variation of the ligation procedure. They injected alloxan either into normal animals or into animals whose pancreatic duct was ligated, and thus an atrophy of the exocrine parenchyma seemed to be achieved. Extracts from these pancreases again appeared to contain normal amounts of the hyperglycemic glycogenolytic substance, tested either on the liver slice system or with the hyperglycemic response in test animals. So it was concluded that the beta cells could not be the source of this factor and that the alpha cells were evidently the source of glucagon. Further support for this opinion came from the observation that islets of birds, whose dark islets are said to be rich in alpha cells, contain large amounts of glucagon.[42]

Attempts to destroy the alpha cells selectively

Definite proof for the alpha cell origin of glucagon, however, could be achieved only if it were possible to produce experimentally a deficiency syndrome similar to that which can be produced for the beta cells with alloxan. This deficiency syndrome should further bring some light on the question of whether the differences in the insulin sensitivity of alloxan diabetes and pancreatectomy diabetes are due to a second anti-insulin factor, probably glucagon, and finally prove the hormonal role of glucagon if it could be shown that injections of this protein ameliorate or abolish the deficiency symptoms.

This goal seemed near when in 1951 vanCampenhout and Cornelis[131] reported that they were able with intracardial and subcutaneous injections of cobaltous chloride to obtain a selective destruction of alpha cells in guinea pigs. They assumed that the observed hyperglycemia following the injection ("excitation initiale") was due to the release of glucagon from the damaged cells. Alpha cell damage after cobaltous chloride injections has since been observed in various animals. However, in spite of apparently high doses the degree of damage varies in different species. Extensive destruction is reported in the guinea pig[131–133] and dog,[134] whereas in rabbits the rather complete destruction of alpha cells reported by several authors[135, 136] was not confirmed by others.[133] Cobaltous chloride is reported to cause no alpha cell damage in the rat.[133] In no animal is the destruction of alpha cells complete. There is still a certain percentage of alpha cells which escape injury and whose histologic appearance is normal.[131, 133–136] Although a certain number of these cells seem to be destroyed completely and to disappear from the islets, in the majority of the alpha cells only a hydropic degeneration with swelling of the cells and slight nuclear changes occurs. There is no immediate necrosis of the nuclei similar to the picture in beta

cells after alloxan injection. Furthermore, the alpha cell damage is only transitory, since several days after discontinuance of the cobaltous chloride the alpha cells seem to regenerate and the islets again show a normal pattern.[133, 137]

It has been impossible to cause complete destruction by increase of the dosage because of severe toxic manifestations in the central nervous system (convulsions), the exocrine parenchyma of the pancreas, the liver (fatty degeneration), adrenals, and gastric mucosa.[133]

Changes in the blood sugar curve after cobaltous chloride injection have been found. There is either no increase or only a small rise of the blood sugar in guinea pigs,[131, 133] a very marked one in rabbits,[135-137] and dogs,[134] and no significant change in the blood sugar in rats.[133] In none of the species examined so far has hypoglycemia occurred.[131, 133, 137] No blood sugar depressing effect has been found in alloxan-diabetic animals.[134, 136, 137]

The incompleteness of alpha cell destruction with cobaltous chloride was rather disappointing. Therefore there was hope that another preparation, introduced into experimental studies of the alpha cells by Davis[138] in 1952, would give better results. The substance, a guanidine derivative (decamethylene-diguanidine hydrochloride), was known as synthalin A and for a time had been used in the treatment of diabetic patients, since Frank and his co-workers, who synthesized the drug, reported its blood sugar lowering effect in normal and depancreatized animals.[139, 140] Its use in human diabetics was, however, abandoned, since it had serious toxic effects. Synthalin A causes changes in the pancreatic alpha cells similar to those produced by cobaltous chloride. Here again the destruction is not complete and only a small fraction of the hydropic degenerate alpha cells show nuclear changes which can be interpreted as pyknosis and necrosis. In some instances slight alterations of the beta cells occur.[138] In rabbits there are marked hydropic changes approximately sixteen hours after the injection.[138] That regeneration of damaged alpha cells after synthalin A injections has not yet been reported may be due to the extreme difficulty in keeping alive the animals after this severe intoxication.

Synthalin A has a severe toxic effect on the kidneys, where a variable but usually severe necrosis of the proximal convoluted tubules takes place.[138, 141] The second organ affected is the liver; hydropic changes in the periportal region of the liver lobules sometimes correlate with the degree of alpha cell hydrops. The kidney damage is said to produce a severe uremia which causes death of the animal.[138]

The blood sugar curve after synthalin A differs considerably from the one after cobaltous chloride. Whereas with the latter preparation no hypoglycemia is found, with the former a shorter or longer hyperglycemic episode is followed by a rather profound hypoglycemia which sometimes makes it necessary to inject glucose to keep the animals alive.[138]

It has been reported that the severe hyperglycemia of alloxan-diabetic rabbits is lessened after synthalin A injections. In these animals there has been noted a trend toward ketonemia and ketonuria, which has been interpreted as due not only to changes in the level of liver glycogen but also to an additional factor, namely the destruction and functional impairment of the alpha cells.[136]

The experimental destruction of alpha cells should have some influence on the glucagon content of the pancreas if one assumes that this protein originates from this cell type. Vuylsteke, Cornelis, and deDuve[142] and also Eser and Tüzinkam[132] report that after cobalt treatment a hyperglycemic glycogenolytic factor, assayed with the semiquantitative methods of the liver test slice or the intravenous blood sugar response, is diminished or absent in the pancreatic extracts. Fodden and Read,[143] however, discovered an appreciable amount of this factor in cobalt-treated animals and an even higher amount in cobalt-treated alloxan-diabetic rabbits. In normal and alloxan-diabetic rabbits treated with synthalin A, however, they report none of this material.

Possible extrapancreatic sources of glucagon

One of the criteria of a hormone is that it is produced in a well characterized organ by a well characterized cell type. Doubt as to the specificity of the hyperglycemic factor became evident when an apparently identical factor was found not only in the pancreas of several species but also in the upper two-thirds of the gastric mucosa in dogs and rabbits. Smaller but significant amounts were detected also in the duodenum and ileum of dogs. The gastric mucosa of hogs, sheep, and cattle was apparently free of it. It was suggested that certain silver-stained cells in these locations might be the source of glucagon, all the more since it was known that alpha cells may be demonstrated with certain silver methods.[110]

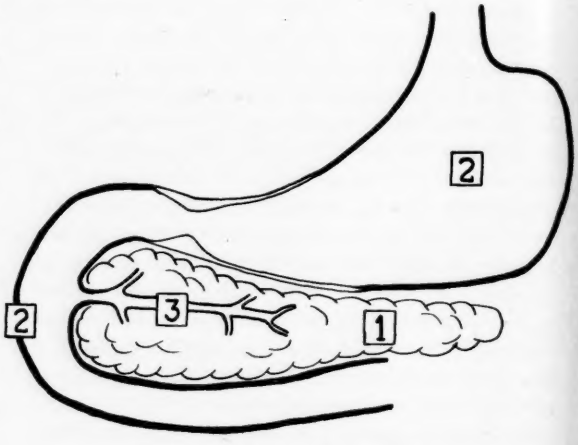
Indeed, in anatomic and pathologic research of recent times there is a tendency to link together certain cells and cell systems which are found in the gastric mucosa,[144] the intestinal mucosa,[145-147] the excretory ducts of the pancreas,[19] and the exocrine parenchyma of the pancreas.[19] Defenders of this idea point out that there

is some evidence for it from the standpoint of embryology, since the anlage of the pancreas is formed first from outgrowths of the primitive gut. Actually at the ostium of the major pancreatic duct these systems are linked together, and here they are not distinguishable from each other[19] (figure 3).

What are these cell systems? The first one, which extends from the lower part of the esophagus throughout the gastrointestinal tract, is known as the enterochromaffin system.[19, 23, 144–147] It consists of cells which are located in the basal parts of the mucosa, giving various histologic and histochemical reactions. One type of positive staining reaction is achieved with the silver methods discussed above. Unfortunately, since the distinction between argentaffin and argyrophil types of cells has not always been applied and almost every author has his own nomenclature for these cells, great confusion has resulted in the literature.[18] To confuse the issue further, not all enterochromaffin cells are argentaffin and argyrophil at the same time. There are some which are only argentaffin, others which are only argyrophil, and still others which are both argentaffin and argyrophil.[18, 19, 148] Ersparmer[149] suggests that this indicates the presence of a developmental cycle. He believes that the pure argyrophil cell is a more immature one, followed by the argentaffin plus argyrophil cell, and that the pure argentaffin cell is the mature cell type. He believes that the argentaffin substance is his "enteramine," a substance which recently has been identified as 5-hydroxytryptamine.[150]

At the papilla of Vater, the ostium of the major pancreatic duct, the enterochromaffin cells of the duodenal mucosa merge almost indistinguishably with those located at the base of the duct epithelium of the pancreas. The cells of the latter system, termed by Feyrter "das insuläre Gangorgan" (insular duct organ),[19] have some similarities to the cells of the enterochromaffin system. However, they exhibit some staining reactions in addition to those observed in the enterochromaffin cells, and on the other hand seem to lack some of those shown by the enterochromaffin cells. Some of the cells of the insular duct organ give staining results similar to those in islet cells, and this is the reason why the whole system was so named. During embryonic life this system (or at least part of it) seems to play an important role in the islet formation (see above), and in later life it seems to have a part in regenerative attempts of the organism to form new islets, as in diabetes. Under pathologic conditions it seems to be of some importance for the genesis of certain tumors of the pancreas.[19]

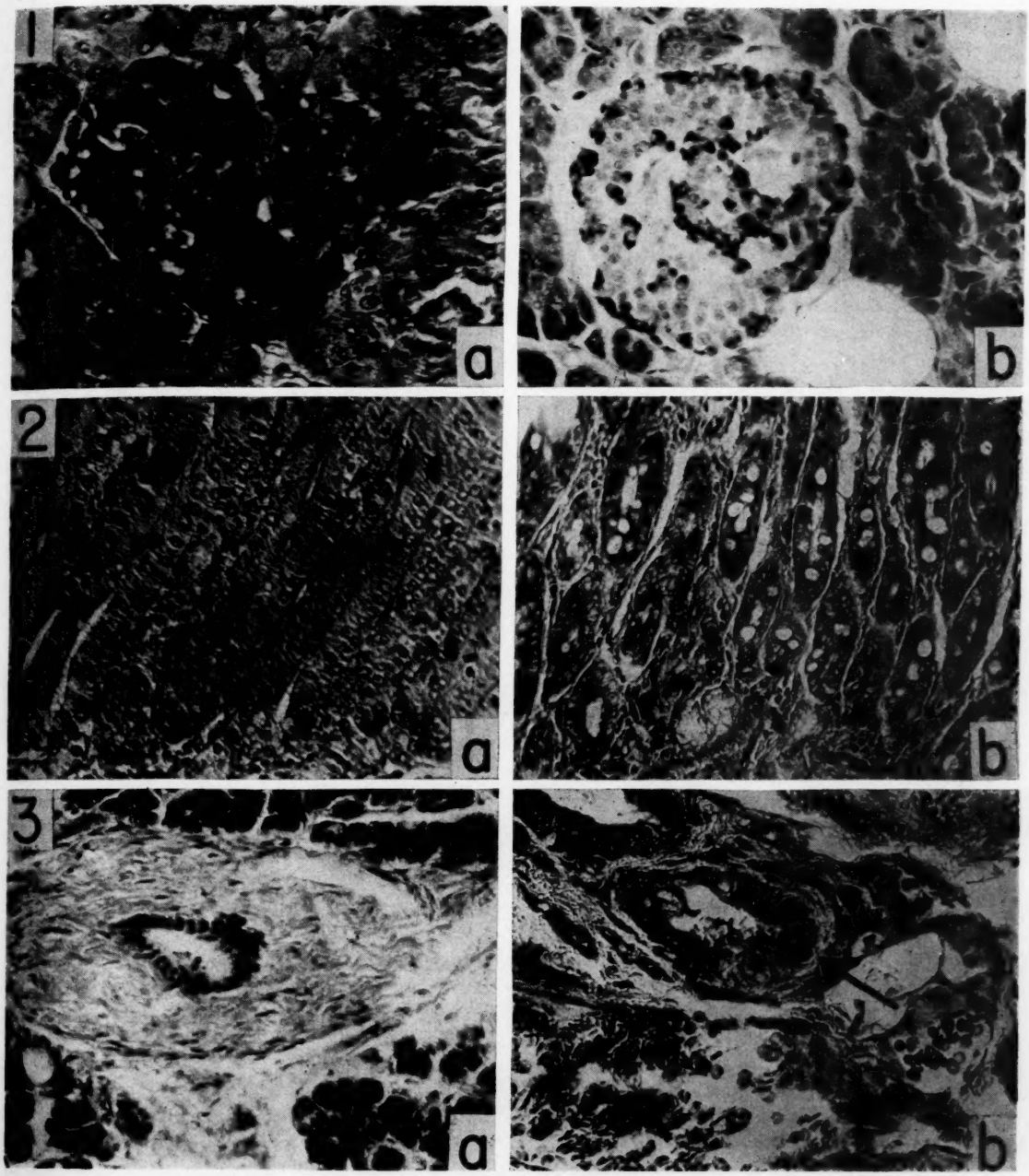
Certain cells scattered through the exocrine parenchyma of the pancreas[58, 151–153] are regarded by some[19, 38] as a link between the cells of the insular duct organ and the cells of the islets of Langerhans proper. They are even called "scattered islet cells" since they give the same or nearly the same staining reactions as islet cells.



Sites of Origin of "Glucagon"
(or Similar Hyperglycemic-Glycogenolytic Factors)

FIG. 3. Diagrammatic representation of supposed sites of origin of glucagon or glucagon-like substances, with corresponding photomicrographs (see opposite page).

Ferner[38] is of the opinion that the alpha cells of the islets and (argyrophil) silver cells in the pancreatic acinar tissue, the insular duct organ of Feyrter, and the enterochromaffin system are absolutely identical. He uses even the expression "alpha cells of the gastric mucosa." He believes that these extrainsular "alpha cells" as well as the alpha cells of the islets produce glucagon.[38, 154] Gaede and Ferner[154] believe that they have demonstrated glucagon in the insular duct organ of the horse, in which pancreatic ducts are comparatively easy to prepare and separate from the acinar tissue. Feyrter[19] is of the opinion, however, that extrainsular islet cells, although similar in various respects, are not essentially the same as islet cells proper. He thinks that differences in location imply different functions. He hypothesizes that the cells of his insular duct organ have three different functions: an endocrine (glucagon production?), a "parakrine," for example, an influence on (exocrine?) cells in the surrounding tissue, and an exocrine function.



The above photomicrographs are numbered to correspond to the numbers on the diagram (*opposite page*).

1. (a) Island of Langerhans, guinea pig, Gomori's aldehydefuchsin and trichrome. Beta cells appear black, alpha cells grey, in photograph. (b) Island of Langerhans, human. Bouin fixation, Bodian silver stain. "Silver cells" black.
2. (a) Duodenum, guinea pig. Gomori's silver methenamine. Enterochromaffin cells black. (b) Duodenum, guinea pig. Pearse's adrenochrome method. Enterochromaffin cells appear black (orange in original stain).
3. (a) Pancreatic duct, human. Bodian silver method. "Silver cells" black. (b) Pancreatic duct, guinea pig. Pearse adrenochrome method. Chromaffin cell black (arrow).

INTERPRETATION OF EXPERIMENTAL DATA

A superficial interpretation of the observations and experimental data of the literature could lead and actually has led to the view that the role of alpha cells as producers of glucagon is proved.[107] When, however, one applies a critical attitude to the results of experimental work which seem at first glance to prove this role, a great gap between actual knowledge and assumptions becomes evident. In recent times various papers have appeared which indicate this gap. They, together with partly unpublished data obtained in this laboratory, are discussed in the following section.

Relation of enterochromaffin and alpha cells

The alleged identity of alpha cells with certain cells of the enterochromaffin system, which would explain the extrapancreatic site of origin of glucagon,[38, 110] has been attacked recently by various authors.[18, 19, 155, 156] Results obtained in this laboratory[76] in human, guinea pig, and rabbit material indicate that these cell types differ considerably in their histochemical behavior. Positive staining results in both cell types could be obtained only with argyrophil methods, whereas the argentaffin reaction of enterochromaffin cells was not given by alpha cells. Of "plasma stains" for the demonstration of alpha cells, only azocarmine B and G gave positive results in both cell types. A whole list of histochemical procedures indicating the presence of SH-groups and other reducing substances, phenols and related substances, and "adrenochromes" in some of the enterochromaffin cells gave essentially negative results in alpha cells. The alpha cells are also outstandingly inert to other histochemical procedures. The tentative suggestion of Dempsey[157] that the alpha cells might contain alkaline phosphatase could not be confirmed. Some blackening occurred in some sections, but it could be interpreted as due to diffusion from blood vessels. A single positive result for acid phosphatase could not be confirmed. On the basis of claims of Ferner[38] that the alpha cells give a positive reaction for ascorbic acid with the aid of the silver nitrate method of Giroud and Leblond, and in view of the experimental production of diabetes with dehydroascorbic acid, numerous attempts were made to elicit this reaction, but without success.

The mere fact that both cell types stain with argyrophil silver methods and azocarmine B and G cannot be supposed to have any histochemical or functional significance. Both methods have a questionable value for a truly selective demonstration of alpha cells, and particularly the use of the former has been attacked by various authors.[31–33]

A further objection to the identity of alpha cells and enterochromaffin cells is the lack of hydropic degeneration in the latter after experiments interfering with the function of alpha cells. Neither after cobaltous chloride injections nor after synthalin A injections did a change occur in enterochromaffin cells similar to that observed in alpha cells.

These observations confirm similar findings of Fodden[155] and Davis.[156] Ferner's statement as to the identity of alpha cells and "silver cells" of the gastric mucosa does not therefore seem to be justified.[38, 46] His hypothesis that extrainsular silver cells play a certain role in the pathogenesis of diabetes seems extremely doubtful. The number of such silver cells does not seem to be increased but decreased in diabetes,[158] and a survey of tumors consisting of these cells (carcinoids) did not reveal a greater incidence in diabetic persons than in the general population.[159]

Clarification is needed particularly as to the lack of correspondence of the sites in which a hyperglycemic-glycogenolytic substance has been found in the gastrointestinal mucosa with the distribution of the enterochromaffin cells and certain silver cells. It has been suggested that a relatively restricted area of certain silver cells in the hog's gastric mucosa has been overlooked in the preparations and therefore glucagon was not found in this animal.[160] This, however, does not explain why a hyperglycemic-glycogenolytic factor has not been found in areas of the gastric mucosa other than the fundic region. Cell types similar to the one to which production of this factor is attributed are without doubt present in the fundic region as well as elsewhere.

Questionable identity of pancreatic extracts

One possible explanation could be that the factor extracted does not have anything to do with glucagon. This possibility must be kept in mind, since in the gastrointestinal mucosa as well as in the pancreatic ducts various cell types can be found which could be capable of producing substances related to adrenalin and thus suggest erroneously the presence of glucagon.[161–164] Indeed, the chemical identity of the hyperglycemic-glycogenolytic substance extracted from extrapancreatic sources with the relatively well determined protein glucagon has never been established. The clarification of this problem is important and should be possible at least for the gastrointestinal mucosa, since sufficient amounts of raw material could be secured easily from this source. This would be much more difficult for preparations of the pancreatic duct system.[154] A biochemical determination of amino-acid content, chemical

and physicochemical behavior, etc., of such a substance would certainly add more for the clarification of this problem than the application of the liver slice method or the determination of the blood sugar response in test animals could do alone, since substances tested with the latter methods could be either glucagon or some other substance with similar properties.[165]

The same considerations should be applied when attempts are made to extract glucagon from pancreatic tissue. Here again the identity of the extracted factor (or factors) with blood sugar raising and glycogenolytic properties with glucagon has not yet been established chemically. An interesting and probably enlightening project would be an investigation of the occurrence of glucagon in certain fish islets in which, as already mentioned, there is a good separation of the exocrine and endocrine tissue. At the same time a hint of its endocrine or exocrine origin could be found.

Defects in experimental evidence for site of origin of glucagon

Exclusion of the exocrine origin of glucagon seems theoretically possible from experiments with the ligation of the excretory duct and atrophy of the exocrine tissue. Such experiments have actually been done, and it has been claimed that thus an exocrine origin of glucagon has been excluded.[110, 114] It may be objected, however, that these experiments do not completely exclude the exocrine origin, since the atrophy of the exocrine tissue sometimes is incomplete, and of course other cell elements undamaged by the ligation could be the source of the factor.

The decision as to whether alpha cells or beta cells are the producers of glucagon (if one assumes that glucagon is produced in the islets at all) might at first seem possible with the aid of alloxan. Since alloxan-diabetic animals show hyperglycemia and pancreatic extracts of these animals are reported to contain glucagon or at least hyperglycemic and glycogenolytic substances, it was concluded that this factor is produced in the alpha cells.[110, 114] This conclusion, however, does not take notice of the possibility that the D cells existing in the islets of man and most animals to a varying extent could be the source of glucagon.[6]

The exclusion of one or the other cell types therefore seemed possible only with the aid of such selective (or nearly selective) alpha cell destroying agents as cobaltous chloride or synthalin A. However, experiments carried out in this laboratory[76] confirm the findings of others[131–138] that with these drugs a complete and immediate destruction of this cell type cannot be achieved. Efforts to destroy completely the alpha cells in rabbits and guinea pigs with cobaltous chloride were unsuccessful. Synthalin A was tested in guinea pigs, rats, and hamsters in an average dosage of 12 mg. per kg. of body weight. Since this amount proved to be very toxic, particularly in guinea pigs, the dosage was diminished in various instances to about 3 mg. However, even this low dosage could not be tolerated and animals could not be kept alive for more than three days. In all animals severe necrosis of the proximal tubules of the kidneys occurred. This kidney damage seemed to be the cause of a variable proteinuria. The animals died finally in uremia.

The degree of hydropic degeneration of the alpha cells varied in the guinea pig. Usually with a 12- or 6-mg. per kg. dosage about the same damage took place as after cobaltous chloride injections. Here again no complete destruction of all alpha cells was evident and at least 10 to 15 per cent of alpha cells escaped injury. The nuclei of the damaged alpha cells exhibited only minor changes such as slight increase in size. It is difficult to evaluate how many, if any, of the alpha cells were completely destroyed, since the possibility exists that the "empty spaces" which could perhaps be interpreted as completely dissolved alpha cells are actually only hydropic cells tangentially cut. Glycogen stains revealed no glycogen deposition in hydropic cells. With low doses of synthalin the degree of hydropic degeneration was somewhat less, although not greatly so. In guinea pigs which were killed or died earlier than sixteen hours after the injection of synthalin A (the time interval reported by Davis[138] to be necessary for

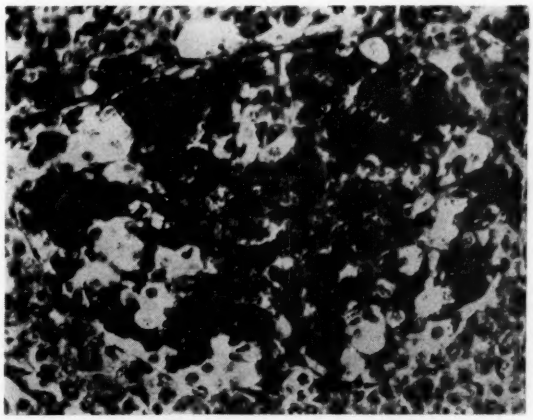


FIG. 4. Guinea pig. Vacuolation of alpha cells due to cobalt. The vacuoles contain neither fat nor glycogen. In our experience complete destruction does not occur. Gomori's aldehyde-fuchsin and trichrome.

the development of hydropic changes in alpha cells of rabbits), slight hydropic changes in the alpha cells were observed as early as four to five hours after the injection, with more severe changes in six to seven hours. In synthalin-treated guinea pigs the blood sugar values, which were hard to obtain because of the smallness of these animals and the fact that their blood clotted very quickly, in the instances where they could be obtained were low in the first ten to twelve hours but normal in those animals which survived or were not killed for two or three days. In general, no attempt was made to influence the blood sugar with dextrose, since in some instances in which this was done at the beginning of the study, intraperitoneal glucose injections did not bring about much improvement in the state of the animals.

In rats and hamsters it was impossible to obtain hydropic changes in the alpha cells with synthalin A injections. Nothing can be said about minor degranulation processes in the alpha cells of these animals, since modern granule stains which give such beautiful results in guinea pigs gave inconclusive findings. Rats and hamsters seem, however, much less sensitive to synthalin A, since in contrast to guinea pigs, rats did not show such severe convulsions. Hamsters survived the injection for eight days but had severe kidney damage similar to that in guinea pigs. In the few instances in which exact blood sugar determinations could be made, hypoglycemic values were not found. A tendency to show an elevated blood sugar (about 200 mg. per 100 cc.) until death was observed in hamsters. No evidence of beta cell damage was observed. The nuclei of beta cells and the beta granules appeared normal compared with normal controls.

The conclusion that blood sugar changes observed after cobaltous chloride and synthalin A injections are due to damage of the alpha cells is probably not permissible. It was thought that the slight hyperglycemia seen following the injection of cobaltous chloride is due to a release of glucagon from the damaged alpha cells.[131] This was, however, doubted by others[6, 134, 135] who found after repeated cobaltous chloride injections that this effect could still be observed although the alpha cells already were damaged. It has been thought that, according to the hypothesis that glucagon is produced in certain enterochromaffin cells, these could be responsible for this effect. An extensive extirpation of the pancreas, stomach, and duodenum up to the ligament of Treitz in dogs was performed, and still a hyperglycemic blood sugar response after cobaltous chloride in these animals was observed. It was therefore concluded that this hyperglycemia could not be due to glucagon.[134] One might object that the last possible source, namely the enterochromaffin cells of the ileum in this experiment, have not been removed. This reasoning seems to have but little significance, since it has been reported recently that the hyperglycemia caused by cobaltous chloride is suppressed by dihydroergotamine, a sympathico-blocking agent, whereas the hyperglycemia and glycogenolytic action on liver slices caused by glucagon are not.[166] This seems to indicate that the cobalt hyperglycemia is not due to glucagon.

Investigations on blood sugar changes after synthalin A with the simultaneous administration of dihydroergotamine have not yet been carried out. However, it is doubtful that the changes would be caused by the damage to the alpha cells. It seems more likely that the severe toxic necrosis of the proximal tubules of the kidney and perhaps toxic manifestation in the liver[138] are responsible for the changes in the blood sugar curve.

The mechanism of hydropic degeneration in alpha cells after cobalt and synthalin A injections is not yet understood. More recent observations seem to indicate that these changes are secondary ones and probably not caused by an action of cobalt or synthalin on the alpha cell itself. Studies with radioactive cobalt indicate a high concentration of this element in the liver and the pancreas. However, radioautographs showed that cobalt was confined in the pancreas to the acinous tissue, whereas the islets of Langerhans seemed free of radioactive material.[167] Creutzfeldt and Schmidt[133] have recently observed vacuolization with hyaline and lipid deposits in the pancreatic acinar tissue of the cobalt-treated guinea pig; similarly, fatty degeneration of the liver with coexisting alpha cell hydrops[69, 81] has been reported by others. Thus it seems possible that the hydropic degeneration is only a result of changes in tissues other than the islets of Langerhans. The relatively long time interval between injections of cobalt and synthalin A and the occurrence of alpha cell hydrops seem to support this view.

The study with radioactive cobalt which revealed that relatively great amounts of cobalt are concentrated in the acinar tissue of the pancreas makes it doubtful that the diminution of extractable hyperglycemic factor of cobalt-treated animals[132, 142] is actually due to the destruction of alpha cells. Since it is known that cobalt has very strong complexing properties, a decrease in the extractable amount of this factor could have been feigned by the formation of a complex compound of the factor with the simultaneously extracted cobalt. Similar considerations as to whether lack of glycogen-

olytic and hyperglycemic factor in pancreatic extracts of synthalin A treated animals is due to lack of glucagon or presence of synthalin A in these extracts should be applied to the report of Fodden and Read.[143]

Why cobaltous chloride and synthalin A cause hydropic degeneration of the alpha cells in one species but not in another is yet unexplained. Even in guinea pigs, in which a rather extensive destruction may be accomplished in some animals, cobaltous chloride does not seem to be effective in pregnant animals.[131] An observation which has been made in our laboratory seems to fit in this line. In two-day-old guinea pigs it was not possible to obtain the slightest degranulation of the alpha cells with cobaltous chloride, even in a dosage of 50 mg. per kg. of body weight.[76]

It seems, therefore, that experiments carried out with synthalin A and cobaltous chloride are at the moment not able to decide the question whether the alpha cells are actually producers of glucagon, since an absolute deficiency syndrome of this cell type has not been established. Similarly this question cannot be decided by assays of hyperglycemic and glycogenolytic materials from the pancreases of normal, duct ligated, alloxan-, cobalt- and synthalin-treated animals, and other sources, unless the chemical identity of these materials with glucagon is shown. It seems possible that hyperglycemic and glycogenolytic properties of such extracts have been erroneously interpreted as being due to glucagon. The role of substances similar to adrenalin must be considered particularly, since it is known that adrenalin and adrenalin-like compounds are apt to initiate a similar glycogenolytic action in liver slices.[161-163] The application of dihydroergotamine with its sympathico-blocking properties seems promising for their differentiation from the action of glucagon. A similar differentiation of the glucagon effect from the effect of other substances with action on the blood sugar in test animals is not yet available. However, the possibility that a glucagon effect is counterfeited by various hormones such as the growth hormone, corticotropin, thyroid hormone, and adrenalin must be considered. There is some recent evidence that the so-called primary hyperglycemia of insulin is due to sympathic stimulation since it may be depressed by dihydroergotamine.[168, 169]

The role of glucagon as an anti-insulin hormone or a diabetogenic agent seems not yet proved. Reports of an insulin-inhibiting action of this protein, based on observations in peripheral tissues, may be evaluated in a different light, if the observation of Goldner[170] that glucagon is inactivated or destroyed by the liver is confirmed. If this occurs to a sufficient degree, the old hypothesis of Bürger that glucagon acts in a synergistic rather than an antagonistic manner to insulin would gain further support. The cytologic site of origin of this protein, however, remains still obscure.

SUMMARY

1. A critical review of the literature together with a consideration of results of the authors' own experimental work has been made.

2. Selective staining methods have been devised to demonstrate the alpha cells of the islands of Langerhans, but no completely satisfactory method exists. Procedures devised by Gomori appear more reliable than the various silver impregnation methods.

3. There are wide variations in different animal species in the distribution and stainability of alpha cells. The varying figures cited for the percentage of alpha cells in the human pancreas in diabetics and non-diabetics reflect considerable differences in technic and interpretation.

4. Opinions differ concerning the embryology of the alpha and beta cells and whether transition forms exist between these two cell types. The weight of evidence suggests that the alpha and beta cells maintain separate identities.

5. The intimate association of glucagon (HGF) with insulin indicates its origin from the pancreas. Experiments causing atrophy of acinar tissue together with destruction of beta cells by alloxan have suggested that glucagon might originate from the alpha cells of the islets of Langerhans.

6. The hypothesis that the alpha cells are the site of production of glucagon and are thus concerned in the pathogenesis of diabetes has been stressed by many authors. Attempts to prove or disprove this by a selective destruction of the alpha cells (by cobaltous chloride and synthalin A) have so far been unsuccessful, since a complete and permanent destruction of these cells has not been achieved.

7. When a factor having the same hyperglycemic and glycogenolytic properties as glucagon was found also in extrapancreatic tissues, it was concluded that it might originate from certain cells of the enterochromaffin system, regarded as similar to or identical with the pancreatic alpha cells. The similarities between these cell types are, however, only superficial. They differ histochemically and in their response to experimental procedures, for example cobaltous chloride and synthalin A.

8. Clarification of the problem of the site of origin of glucagon will probably be possible only when the chemical identity or lack of identity of various pan-

creatic or extrapancreatic extracts with glucagon can be proved.

SUMMARIO IN INTERLINGUA

Le Natura e le Function del Cellulas Alpha del Pancreas, Includente lor Rolo Possibile in le Production de Glucagon

1. Es presentate un revista critic del litteratura insimul con le description del resultatos obtenite per le autores in lor proprie experimentos.

2. Ha essite disveloppate plure methodos pro le coloration selective del cellulas alpha in le insula de Langerhans, sed nulle de iste methodos es completemente satisfacente. Le technica disveloppate per Gomori es apparentemente plus efficace que le varie methodos a impregnation con argento.

3. In differente species animal il existe grande variationes del distribution e colorabilitate del cellulas alpha. Le varie valores citate in le litteratura pro le procentage de cellulas alpha in le pancreas human in diabeticos e nondiabeticos reflecte considerabile differentias de technica e de interpretation.

4. Varie autores ha varie opiniones in re le embryologia del cellulas alpha e beta e in re le question de si il existe un transition inter iste duo typos cellular. Le balancia del accumulate datos corroborative pare favorir le conception que le cellulas alpha e le cellulas beta mantene identitates separate.

5. Le intime association de glucagon con insulina indica que illo es originari del pancreas. Experimentos in que alloxano causa simultaneemente atrophia de texito acinose e destruction de cellulas beta ha essite interpretate como indicante que glucagon es possibilemente originari del cellulas alpha in le insulas de Langerhans.

6. Multe autores ha favorite le hypothese que le cellulas alpha es le sito del production de glucagon e que illos es assi involvite in le pathogenese de diabete. Essayos a provar o disprovar iste hypothese per le destruction selective del cellulas alpha (per medio de chlorido cobaltose e Synthalina A) ha usque nunc remanite sin successo, proque le complete e permanente destruction de iste cellulas se ha non ancora effectuate.

7. Post le discoperta etiam in texitos extrapancreatic de un factor que possede le mesme qualitates hyperglycemic e glycogenolytic como glucagon, il pareva possibile concluder que glucagon es originari de certe cellulas del systema enterochromaffin le quales esseva considerate como simile al cellulas alpha pancreatic o mesmo identic con illos. Sed le similaritates inter iste typos cellular es solmente superficial. Iste cellulas differe histochimicamente e in lor responsas in procedimentos experimental a per exemplo chlorido cobaltose e Synthalina A.

8. Il es probabile que le problema del sito de origine de glucagon non va esser clarificate usque on ha succedite a provar o disprovar le identitate chimic de glucagon con varie extractos pancreatic e extrapancreatic.

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The Role of Fat in the Diet

The dietary fat provides for the organism an immediate source of calories, as well as a large available reserve of energy. This latter aspect is important because the capacity to store protein and carbohydrate is relatively limited and the fat depots therefore meet the requirement for an energy reserve. Also of importance is the fact that the caloric value of fat per gm. (9.3 calories) is more than twice that for either carbohydrate (4.1 calories per gm.) or protein (4.1 calories per gm.).

In addition to providing a source of readily available energy, dietary fat serves as a vehicle for introducing the fat-soluble vitamins into the body. The potency of various fats and oils with respect to vitamins A and D has been clearly established, and the other fat-soluble vitamin, E, is present in high concentrations in wheat germ. The presence of these dietary essentials in fats forms a sound basis for the physiologic value of fatty products like butter fat, egg yolk, and cod liver oil, which have long enjoyed a reputation for unique nutritive potency. The normal absorption of the antihemorrhagic vitamin K from the intestine is dependent on a normal flow of bile which is stimulated by food fat. Dietary fat also aids in absorption of minerals.

One of the most important functions of dietary fat is to provide the organism with essential fatty acids.

From the book *Diseases of Metabolism* edited by Garfield G. Duncan, M.D., published by W. B. Saunders Co., Philadelphia, 3rd ed., 1952, Section "Lipid Metabolism" by Abraham White, Ph.D., p. 197.

Quantitative Estimation of the Pancreatic Islet Tissue in Diabetic Subjects

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Many diabetic pancreases, particularly those of the young, exhibit no qualitative changes either in islet or acinar tissue. Quantitative variations are known to affect some of these pancreases but have never been expressed in terms of the weight of alpha and beta cells. This investigation was undertaken in an endeavor to compare the weights of islet tissue in diabetic and nondiabetic subjects.

MATERIAL

Eighty-five diabetic pancreases were weighed at autopsy and examined microscopically. Fifty-five were rejected for reasons detailed in table 1. In the remaining thirty, which were investigated quantitatively, fibrosis of the islets was either absent or of slight degree. Pancreases obtained at autopsies of normally nourished nondiabetic subjects of the same age and sex distribution were used as control material.

UTILISATION OF DIABETIC MATERIAL UNDER REVIEW

	AGE AND SEX DISTRIBUTION									
UTILISATION	MEN	WOMEN	10-	20-	30-	40-	50-	60-	70 & OVER	TOTAL
REJECTED BECAUSE OF a) ACROMEGALY b) ADRENOCORTICAL TUMOURS		2						1	1	2
REJECTED BECAUSE OF HYALINISATION OF ISLETS	8	17				3	4	11	7	25
REJECTED BECAUSE OF UNSATISFACTORY DIFFERENTIAL STAINING	8	20		5	3	3	4	10	3	28
SUITABLE FOR ESTIMATION OF α & β CELL TISSUE	6	24	1	3	1	4	4	11	6	30
TOTAL	22	63	1	8	4	10	12	33	17	85

TABLE 1

METHOD

The intact pancreas was dissected from the surrounding connective tissue, splenic vessels, and bile duct and weighed. Sections from the head, body, and tail of the pancreas taken in its long axis were fixed in Helly's and Bouin's fluids, embedded in paraffin, cut at 3 μ, and stained by hematoxylin and eosin and by the chrome alum hematoxylin phloxin method of Gomori.[1] By means of a calibrated 0.5-mm. squared grid inserted into the eyepiece of a microscope the area of 100 randomly selected islets (33 in the head, 33 in the body, and 34 in the tail) was measured in terms of small squares, and the average was calculated. The distribution of islets was surveyed in sufficient microscopic fields to include 100 islets or the nearest number over 100 in each of the head, body, and tail. Adequate representation was given to the margins of the pancreas where fat tends to accumulate; similarly no attempt was made to exclude fields containing larger blood vessels and ducts. With these provisos, as wide an area as possible was sampled in each section. The proportion of islet tissue in the pancreas could now be estimated. For the purpose of the investigation, the specific gravity of the acinar and islet tissues, the interstitial tissues, and the blood vessels and ducts was assumed to be the same, an approximation unlikely to lead to a grave miscalculation except in a very fatty pancreas.

$$\text{The proportion (P) of islet tissue in the pancreas} = \frac{\textit{Average area of an islet} \times \textit{number of islets per microscopic field}}{\text{Total area of microscopic field}}$$

If W be the weight of the pancreas, then the weight of islet tissue

$$= \tfrac{1}{3}\,[\text{WP (head)} + \text{WP (body)} + \text{WP (tail)}].$$

A differential count of approximately 2,000 to 2,500 islet cells fairly equally distributed between head, body, and tail was made on sections stained by Gomori's chrome hematoxylin phloxin method. (Delta cells in this method are not differentiated from the alpha cells and are included with the alpha cell count.) Assuming that one-fifth of the islet tissue consists of blood vessels and tissues other than alpha and beta cells (Wrenshall, Bogoch, and Ritchie),[2] then

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Weight of beta cells = 4/5 weight of islet tissue × percentage of beta cells.

Weight of alpha cells = 4/5 weight of islet tissue × percentage of alpha cells.

Although the primary aim of the method was the assessment of the total weight of alpha and beta cells, some estimate of the total number of pancreatic islets can also be obtained from the data by relating the average volume of an islet to the total volume of islet tissue. Tejning,[3] in his exhaustive analysis of this problem in rats found that the main part of the islet tissue consisted of islets of average size, and that taken together the relatively numerous small islets contained the same amount of islet tissue as the relatively few large islets; the volumetric distribution of islets over different orders of magnitude formed a normal frequency curve. A rough estimate of the total number of islets can, therefore, be obtained from the average volume of 100 islets. The apparent size of the islet seen in cross-section is unlikely to represent the maximum cross-sectional area of the islet, but if it is assumed that the islets are spherical, an approximation to the true radius can be calculated as follows:

$$\text{Observed cross-sectional area} = \frac{\frac{4}{3}\pi r^3}{2r} = \frac{2}{3}\pi r^2$$

where r = true radius of the sphere
Let A = Mean number of squares per islet
S = Area of one square.

$$\text{Then the mean area of an islet} = AS = \frac{2}{3}\pi r^2$$

$$\text{Therefore } r^2 = \frac{3AS}{2\pi}$$

$$\text{Volume of an islet} = \frac{4}{3}\pi \left(\frac{3AS}{2\pi}\right)^{\frac{3}{2}} = \left(\frac{6}{\pi}\right)^{\frac{1}{2}} S^{1\frac{1}{2}} \cdot A^{1\frac{1}{2}}$$

If G is the specific gravity of pancreatic tissue, V is the volume of one islet,
W is the total weight of islet tissue per pancreas,
and N is the total number of islets per pancreas.

$$\text{Then } N = \frac{W}{GV} = \frac{\pi^{\frac{1}{2}}}{G^{\frac{1}{2}}GS^{1\frac{1}{2}}} \cdot \frac{W}{A^{1\frac{1}{2}}} = K\frac{W}{A^{1\frac{1}{2}}}$$

RESULTS

The results detailed in tables 2 and 3 suggest the following conclusions.

Weight of Pancreas

(1) Diabetic pancreases vary more in weight than the controls (figure 1), ranging from the 20-gm. pancreas of a woman of twenty-seven whose diabetes started at the age of thirteen to the large, fatty 118-gm. pancreas of an obese female patient aged seventy-one.

(2) Diabetic pancreases tend to be smaller than

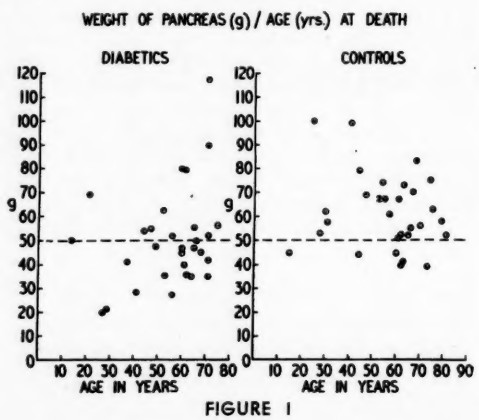

FIGURE 1

nondiabetic pancreases. Sixteen of the diabetic group weigh less than 50 gm., compared with only six of the controls. Similarly, the main concentration falls between 35 and 55 gm. in the diabetic group, whereas in the control group it covers the 50 to 75 gm. range.

(3) The weights of diabetic pancreases tend to increase with age, whereas in the control group there is a tendency to decrease in later life. The weight of the pancreas, in both groups, tends to increase with increasing weight of the body (figure 2). But differences

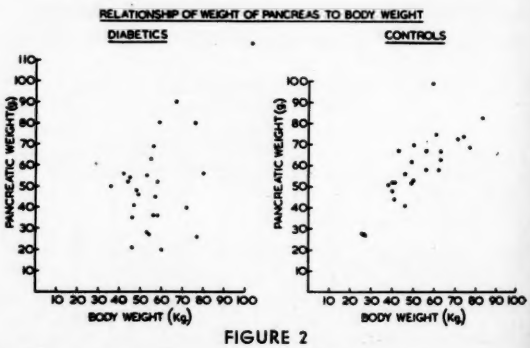

FIGURE 2

in the body weights cannot account for the differences in pancreatic weights in two roughly comparable groups; in the body weight group 40 to 60 kg., eleven of nineteen diabetic pancreases and only three of fourteen controls weigh less than 50 gm.

Weight of Islet Tissue

The weight of islet tissue of diabetics tends to be less than normal. It varies from 0.019 to 1.0 gm. in the diabetics and from 0.57 to 1.89 gm. in the controls (figure 3). Despite a substantial overlap in individual values, the difference between the mean weight of islet tissue in the diabetics (0.45 gm.) and in the controls (1.06 gm.) is highly significant.

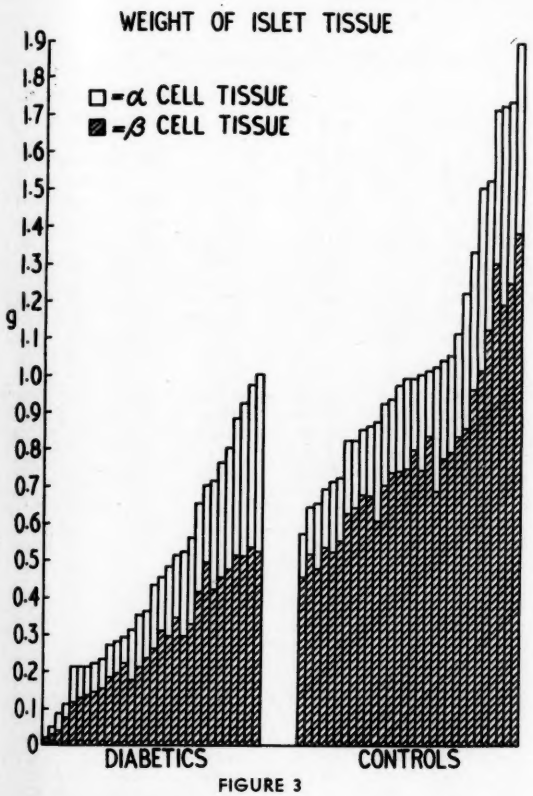

FIGURE 3

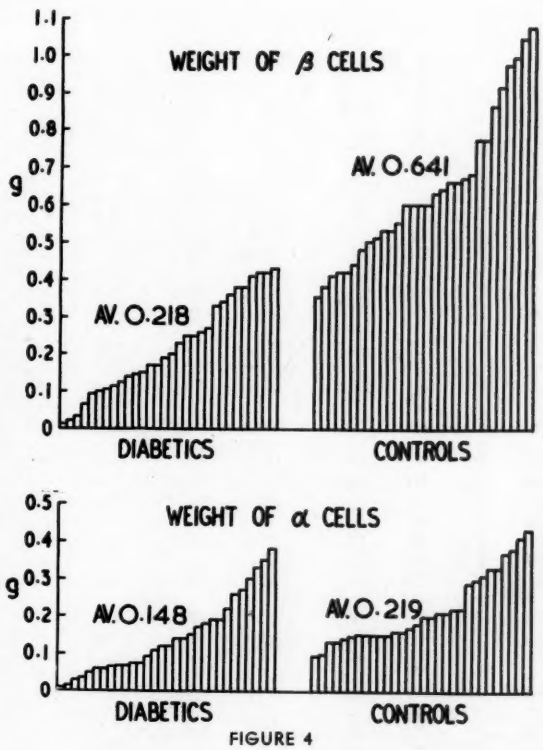

FIGURE 4

Beta to Alpha Cell Ratio

The proportion of beta cells in the islets of the diabetic pancreas is usually reduced at all ages. The beta to alpha ratio in the diabetic cases ranges from 1:1 to 2.3:1, with an average of 1.5:1, whereas in nondiabetics it varies between 2:1 and 4.6:1, with an average of 3:1.

Weight of Beta Cells

The total weight of beta cells in the diabetic pancreas is usually less than normal. It varies from 0.0096 to 0.43 gm., with an average of 0.22 gm., in the diabetics, and from 0.36 to 1.07 gm., with an average of 0.64 gm., in the nondiabetics (figure 4). Despite a highly significant difference in the mean weights of the beta cells in the diabetic and control groups, seven diabetics have greater beta cell values than the lowest control value, whereas five controls have values below the highest diabetic value.

Weight of Alpha Cells

The mean weight of the alpha cells of the diabetic group is significantly less than that of the control group, but the difference is much less striking than in the case of the beta cells (figure 4). In diabetics, the total weight of alpha cells varies from 0.0064 to 0.38 gm., with an average of 0.15 gm., whereas in controls it varies from 0.10 to 0.43 gm., with an average of 0.22 gm. Diabetics with beta cell weights roughly comparable with the lower control values have a much greater quantity of alpha cells than the corresponding controls (figure 3).

Relation of Weight of Alpha and Beta Cells to Duration and Onset of Disease

The duration of disease from diagnosis until death in this series varies from a few days (Case 11) to twenty-four years (Case 21). No correlation exists between the duration of the disease and the weight of beta cells (figure 5), and there is a similar lack of correlation in respect to the alpha cells.

The youngest age at which the diagnosis of diabetes was made was nine years (Case 4) and the oldest seventy-three years (Case 30). Patients developing diabetes during the growing period have very low weights of beta cells, whereas those developing diabetes after maturity have much higher values (figure 6). There is

TABLE 2

Diabetic cases

Case No.	Sex	Age at death	Age at onset of diabetes	Duration of diabetes (years)	Weight of body (kg.)	Weight of pancreas (gm.)	Weight of islets (gm.)	Ave. area of an islet (squares)	Percentage Alpha cells	Percentage Beta cells	Weight of Alpha cells (gm.)	Weight of Beta cells (gm.)	Approximate number of islets in pancreas (in thousands)	
													Total	Per gm. of pancreas
1	F	14	14	6/52	36.0	50.0	0.28	3.8	33	67	0.11	0.15	221	4.4
2	M	22	17	5	56.5	69.4	0.11	2.9	35	65	0.03	0.064	131	1.9
3	F	27	13	14	60.0	20.4	0.046	2.3	46	54	0.017	0.020	84	4.2
4	F	28	9	19	46.0	21.2	0.084	2.8	54	46	0.036	0.031	100	4.7
5	M	37	35	2	46.5	41.1	0.29	2.5	24	76	0.05	0.17	430	10.5
6	F	41	20	21	53.5	28.3	0.019	3.5	38	62	0.0064	0.0096	18	0.6
7	F	44	42	2	45.0	53.8	0.48	3.9	39	61	0.20	0.25	365	6.8
8	M	47	42	5	53.0	54.7	0.51	3.6	33	67	0.136	0.27	438	8.0
9	F	49	49	5/12	47.5	47.6	0.43	3.6	40	60	0.14	0.20	369	7.7
10	F	52	42	10	55.0	62.6	0.27	2.9	33	67	0.068	0.146	320	5.1
11	M	53	53	10 days	56.0	35.5	0.21	3.3	46	54	0.079	0.096	205	5.8
12	F	56	52	4	54.0	27.4	0.22	4.1	35	65	0.061	0.114	155	5.7
13	F	56	52	4	58.0	52.0	0.31	3.6	44	56	0.11	0.14	266	5.1
14	F	60	50	10	Very obese	46.7	0.23	3.4	35	65	0.061	0.121	215	4.6
15	F	60	60	3/12	59.0	80.0	0.88	5.4	42	58	0.30	0.41	411	5.1
16	M	60	60	6/12	49.0	45.6	1.0	3.2	48	52	0.38	0.42	1,025	22.5
17	F	61	41	20	72.0	39.9	0.71	4.8	41	59	0.22	0.34	412	10.3
18	F	61	57	4	76.0	79.9	0.52	3.5	44	56	0.18	0.23	465	5.8
19	F	62	55	7	58.0	36.2	0.35	3.8	41	59	0.12	0.17	277	7.7
20	F	64	61	3	N.N.	35.4	0.22	3.1	40	60	0.067	0.10	236	6.7
21	F	65	41	24	Slightly obese	46.8	0.36	2.7	35	65	0.096	0.19	475	11.1
22	F	65	53	12	80.0	55.6	0.97	6.0	45	55	0.35	0.43	387	7.0
23	F	66	62	4	N.N.	50.0	0.65	4.5	37	63	0.19	0.33	399	8.0
24	F	68	63	5	57.0	44.8	0.76	5.1	41	59	0.26	0.36	387	8.7
25	F	71	58	13	44.0	52.0	0.45	4.7	32	68	0.12	0.25	259	5.0
26	M	71	65	6	66.5	89.5	0.92	5.0	45	55	0.33	0.42	482	5.4
27	F	71	68	3	46.0	35.2	0.80	3.8	41	59	0.27	0.38	633	18.0
28	F	71	69	2	103.0	117.7	0.70	4.4	30	70	0.17	0.38	444	3.8
29	F	71	69	2	N.N.	41.8	0.56	4.4	42	58	0.19	0.26	356	8.5
30	F	75	73	2	42.0	56.3	0.21	2.6	40	60	0.068	0.102	294	5.2

N.N.=Normally nourished.

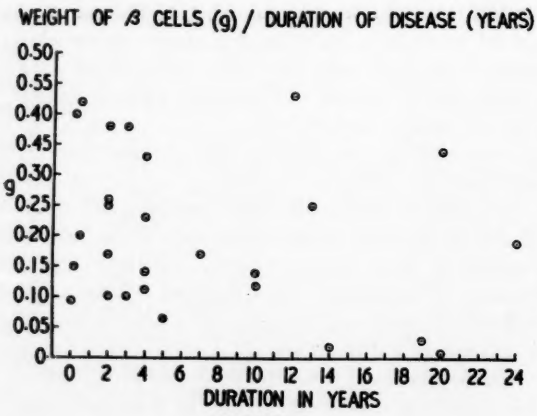

FIGURE 5

also a suggestion, which may not be borne out by further observation, that the beta cell weights in the forty to sixty year group are lower than those in the group over sixty. Similar trends are apparent in the alpha cell weights (figure 7), namely low values for the growth onset type, intermediate values for the middle-aged, and high values for the elderly diabetic.

Number of Islets in Pancreas

The diabetic pancreas usually contains fewer islets than the nondiabetic pancreas. The total number of islets in the diabetics ranges from 18,000 to 1,025,000, with an average of 342,000, and in the controls from 442,000 to 1,447,000, with an average of 857,000 (figure 8). The number of islets per gram of pancreas varies in the diabetics between 600 and 22,500, with an average of 7,130, and in the controls between 6,400 and 23,900, with an average of 14,800 (figure 9).

Size of Islets

The average size of 100 islets was measured in terms of small squares in each of the diabetic and control cases. The mean size in the 30 diabetics is the same as that in the 30 controls, 3.8 squares, but variations

TABLE 3
Control cases

Case no.	Sex	Age at death	Weight of body (kg.)	Weight of pancreas (gm.)	Weight of islets (gm.)	Ave. area of an islet (squares)	Percentage Alpha cells	Percentage Beta cells	Weight of Alpha cells (gm.)	Weight of Beta cells (gm.)	Approximate number of islets in pancreas (in thousands) Total	Per gm. of pancreas
1	F	15	N.N.	44.5	1.05	3.6	25	75	0.21	0.64	901	20.3
2	M	25	N.N.	99.2	1.33	3.8	28	72	0.30	0.77	1,052	10.6
3	F	28	49.5	52.9	0.82	3.7	22	78	0.15	0.51	675	12.8
4	F	29	49.5	63.3	0.85	3.6	21	79	0.15	0.53	729	11.5
5	M	31	56.0	57.6	1.73	4.7	28	72	0.38	0.99	995	17.3
6	F	41	58.5	99.0	0.86	4.0	22	78	0.15	0.53	630	6.4
7	M	44	N.N.	79.4	1.04	3.5	26	74	0.22	0.67	931	11.7
8	F	44	40.0	48.0	0.72	3.7	24	76	0.14	0.44	593	12.4
9	F	47	76.5	69.7	1.52	4.2	25	75	0.31	0.91	1.035	14.8
10	M	54	74.0	74.0	1.00	4.3	26	74	0.20	0.60	657	8.9
11	F	55	43.0	66.8	0.57	2.5	22	78	0.10	0.36	846	12.7
12	F	55	63.0	66.7	1.11	4.4	25	75	0.22	0.66	705	10.6
13	F	57	N.N.	60.4	0.71	3.7	27	73	0.15	0.42	584	9.7
14	F	60	41.0	44.5	0.99	3.1	20	80	0.16	0.63	1,063	23.9
15	F	61	38.5	50.7	1.02	3.7	33	67	0.37	0.77	840	16.6
16	F	61	55.6	66.7	0.65	4.2	27	73	0.145	0.38	442	6.6
17	F	62	Thin	39.5	0.87	3.5	31	69	0.21	0.48	778	19.7
18	F	62	40.5	51.8	0.93	2.9	21	79	0.16	0.60	1,103	21.3
19	F	63	45.7	40.6	0.82	3.2	24	76	0.15	0.50	840	20.7
20	F	63	71.5	73.0	1.72	5.9	31	69	0.43	0.97	703	9.6
21	F	65	49.0	52.0	1.89	5.2	27	73	0.41	1.07	934	18.0
22	M	66	N.N.	54.8	0.69	3.3	23	77	0.13	0.41	675	12.3
23	F	67	50.0	70.2	1.50	5.1	28	72	0.33	0.86	763	10.9
24	F	68	83.0	83.4	0.99	3.5	25	75	0.20	0.60	886	10.6
25	F	70	46.0	55.5	1.01	3.5	18	82	0.13	0.66	904	16.3
26	F	73	Thin	38.9	0.97	3.6	24	76	0.18	0.60	832	21.4
27	M	74	60.5	74.6	0.92	3.6	24	76	0.17	0.55	789	10.6
28	F	75	63.0	63.0	1.22	2.9	30	70	0.29	0.68	1,447	23.0
29	F	77	62.0	58.1	0.64	2.0	20	80	0.10	0.41	1,325	22.8
30	F	81	40.0	52.1	1.71	4.5	24	76	0.33	1.04	1,049	20.1

N.N.=Normally nourished.

within the groups are revealed by scatter diagrams. Whereas the size of the islets in the diabetics tends to increase with age of the patient, in the control group it tends to decrease with age. Statistical analysis confirms the presence of a positive correlation between islet size and age in the diabetics significant at the 1 per cent point, but the relation between islet size and age in the controls is not significant. The islet size, however, also tends to increase with increasing weight of the patient, and since the weight of the older diabetics tends to be greater than that of the younger ones, allowance must be made for this factor.

When $\frac{\textit{Islet size in squares} \times 10}{\text{Body weight in kg.}}$

is plotted against the age at death in the twenty-four cases where the body weight was known (figure 10), a positive correlation between islet size and age in the diabetic cases is still apparent. Furthermore, statistical analysis shows that when age is taken into account, the residual correlation between islet size and body weight is insignificant.

DISCUSSION

Quantitative Variations in the Diabetic Pancreas

An obstacle to the elucidation of the pathogenesis of diabetes mellitus in man is the apparent lack of correlation between the clinical manifestations of the disease and the pathologic findings. Thus, Warren and LeCompte[4] found that the islets in one-third of 811 diabetic pancreases were histologically normal. Nevertheless, there is much to suggest quantitative variations in the diabetic pancreas. Thus, the pancreas may show reduction in weight (Weichselbaum,[5] Kraus,[6] Vartiainen[7]); abnormally few islets (Ssobolew,[8] Sauerbeck,[9] Cecil,[10] Weichselbaum,[5] Heiberg,[11,12] Conroy,[13] Kraus[6]); a subnormal proportion of islet tissue (Weichselbaum,[5] Susman[14]); and a reduced beta to alpha cell ratio of the pancreatic islets (Gomori,[1] Ferner,[15,16] Terbrüggen[17]).

With these conclusions our findings are in broad agreement. The quantitative alterations in the pancreas, although varying in their incidence and severity, usually tend to reduce the amount of beta cell tissue. Table 4 shows the approximate influence of the quantitative

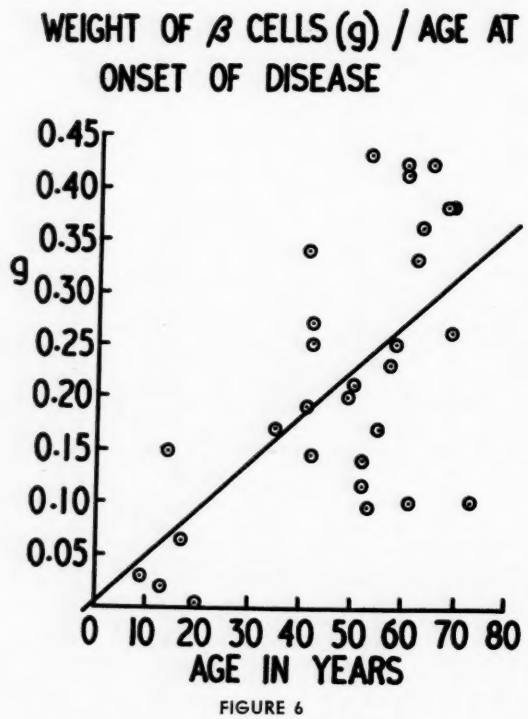

FIGURE 6

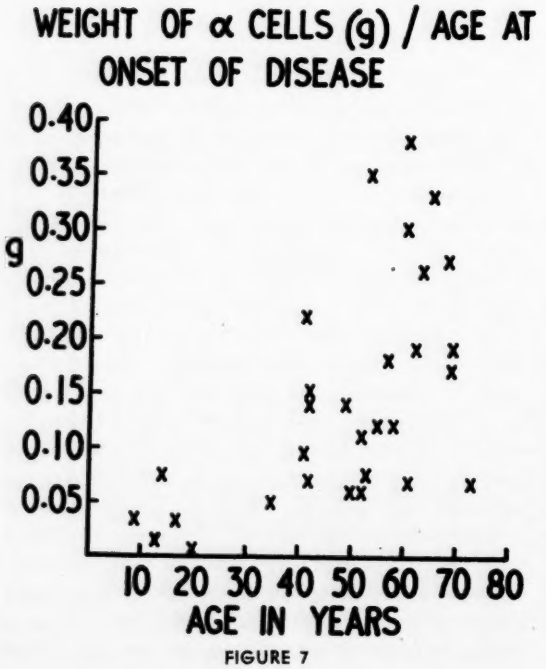

FIGURE 7

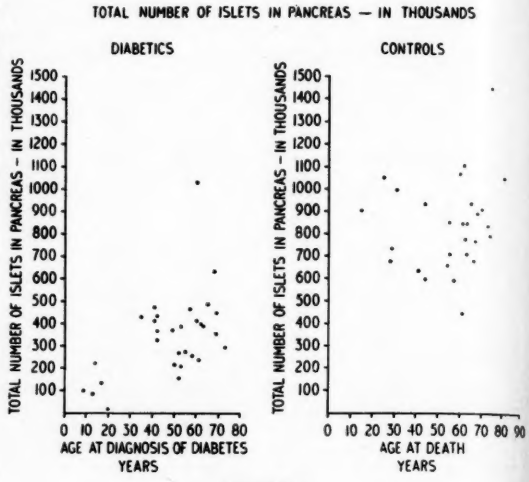
TOTAL NUMBER OF ISLETS IN PANCREAS — IN THOUSANDS
DIABETICS
CONTROLS
TOTAL NUMBER OF ISLETS IN PANCREAS - IN THOUSANDS
AGE AT DIAGNOSIS OF DIABETES YEARS
AGE AT DEATH YEARS

FIGURE 8

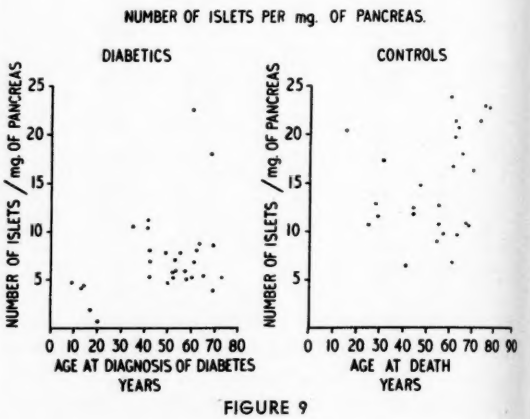
NUMBER OF ISLETS PER mg. OF PANCREAS.
DIABETICS
CONTROLS
NUMBER OF ISLETS / mg. OF PANCREAS
AGE AT DIAGNOSIS OF DIABETES YEARS
AGE AT DEATH YEARS

FIGURE 9

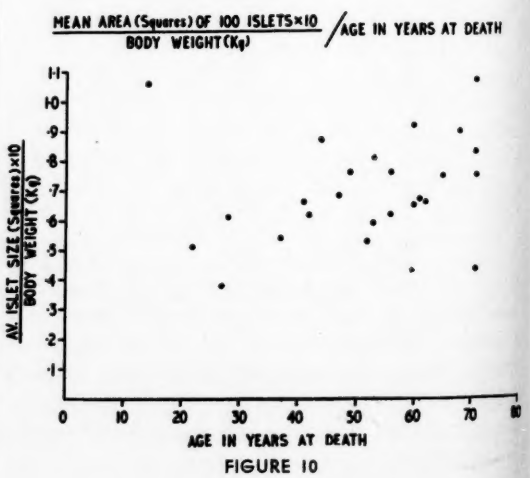
MEAN AREA (Squares) OF 100 ISLETS×10 / BODY WEIGHT (Kg)
AGE IN YEARS AT DEATH
AV. ISLET SIZE (Squares)×10 / BODY WEIGHT (Kg)
AGE IN YEARS AT DEATH

FIGURE 10

variations in the present series.

TABLE 4

	Proportion of Control Values	
	Growth onset diabetic cases (5)	Maturity onset diabetic cases (25)
Weight of pancreas	3/5	6/7
Proportion of islet tissue in pancreas	1/6	3/5
Beta to alpha cell ratio in pancreatic islets	4/5	4/5

The possibility that insulin deficiency might be mainly due to a quantitative deficiency in the beta cells obviously needs exploration, since recent evidence strongly suggests that there is a difference in the amount of available insulin in the two types of disease. Thus, Bornstein and Lawrence,[18] assaying the plasma insulin of diabetic subjects by means of alloxan-diabetic-adrenalectomized-hypophysectomized rats, were able to classify their cases into (1) those patients, mainly young, in whom the diabetes was severe, with weight loss and ketosis, and (2) the middle-aged, obese, commonly female diabetics with no ketosis or loss of weight. In the first group no plasma insulin was demonstrable, whereas in the second group roughly 70 per cent of normal control values were obtained. Again, Wrenshall, Bogoch and Ritchie,[2] in assays of the insulin extractable at autopsy from the pancreases of 64 diabetics and 149 nondiabetics demonstrated that the extractable insulin was lower in diabetics than in controls dying from the same assigned cause; it was very low in subjects developing diabetes during the normal period of growth (growth onset type), and was much higher in the majority of subjects developing the disease after maturity (maturity onset type). In figure 11 our data for the weight of beta cells per gram of pancreas have been added to one of their figures comparing the amount of extractable insulin per gram of pancreas in diabetics and controls in each of four age groups. Similar trends are seen in both series: low values for extractable insulin and beta cell weights in growth onset diabetics, and values on the average roughly about half those of the controls in maturity onset diabetics. It therefore seems likely that, irrespective of any degranulation of beta cells, the reduction in quantity of beta cell tissue may account substantially for the reduced insulin content of the diabetic pancreas. This is of considerable importance since Young[19] has re-emphasized that the effect of anterior pituitary extract varies with the availability of insulin; if the pancreatic

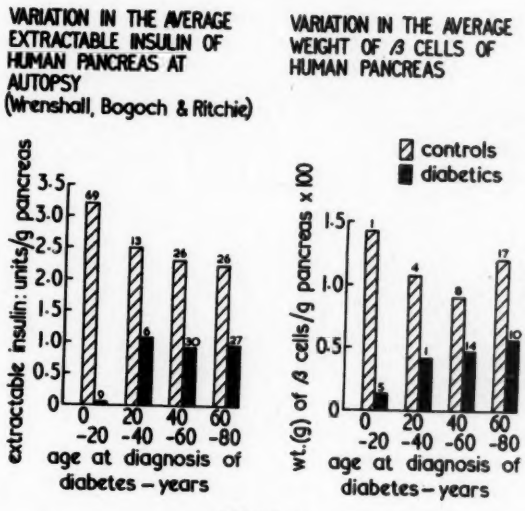

FIGURE 11

secretion of insulin is deficient, then protein breakdown and glycosuria may occur. Marks and Young[20] have also confirmed, in diabetic dogs, the clinical observations of Petrén[21] that breakdown of protein, especially muscle protein, is particularly associated with and largely responsible for the appearance of ketonuria. Thus, differences in ketotic tendencies between young and older diabetics may be largely accounted for by quantitative differences in beta cell tissue and available insulin.

Insulin Sensitivity

The diabetic syndrome, however, cannot be explained simply in terms of insulin deficiency. Himsworth[22] divided diabetes into the insulin-sensitive type usually starting as an acute disease in the young, and the insulin-insensitive type of insidious onset commonly affecting the elderly. He noted that in response to insulin there was little uptake of glucose by the tissues of the insulin-insensitive diabetics, whereas there was a distinct increase in uptake in the insulin-sensitive diabetics. Bearn, Billing, and Sherlock[23] also demonstrated a difference in the hepatic glucose output in response to insulin in the two types. Young[24] has suggested that both forms of the disease may be caused by hyperactivity of the pituitary gland, the insulin-sensitive type resulting from a short period of hypersecretion of growth hormone with subsequent return to normal pituitary function, whereas a slightly excessive rate of secretion of growth hormone over a long period of time might ultimately result in the development of obesity and diabetes. In this connection, Blumenthal[25] found

considerable variation in the adrenotrophic activity of the human hypophysis in relation to age, with peaks in the age groups 11 to 20 and 61 to 70 years. Although the variation in the growth hormone content of the hypophysis of man is not known, it is entirely reasonable to suppose that the activity is high during the growing period. A period of intense pituitary overactivity might, therefore, precipitate a diabetic state which rapidly progresses to coma requiring massive doses of insulin for its control (idiohypophysial diabetes) and result in irrecoverable damage to the pancreatic islets. If the duration of marked pituitary hypersecretion was relatively short, patients surviving it, although permanently diabetic (metahypophysial diabetes), would again become insulin-sensitive. The similarity, both in insulin sensitivity and low pancreatic insulin content, between the metahypophysial dog (Marks and Young,[20]) and the growth onset diabetic patient is clear. The relationship between pituitary activity and the diabetes of later life is less obvious, but the development of diabetes in females 1 to 46 years (average 24 years) after the birth of an abnormally large baby (Kriss and Futcher[26]) certainly lends support to the concept of prolonged pituitary hypersecretion as a causative factor. If such is the case, then prolonged, slightly excessive pituitary secretion might cause pituitary islet imbalance with slow degeneration of the beta cells and reduction in the beta to alpha cell ratio. This would ultimately result in diabetes which, if the pituitary hypersecretion continued, might be relatively insulin-insensitive. Furthermore, since hyperplasia of islet tissue is known to accompany growth induced by anterior pituitary extract (Richardson and Young,[27] Ham and Haist,[28] Ogilvie[29, 30]) some enlargement of islets might be expected to occur in older diabetics. The steady increase in islet size with age in the present series of diabetics (figure 10) is, therefore, in keeping with Young's views on the influence of the pituitary in the causation of diabetes.

Role of Alpha cells

The function of the alpha cells has recently been reviewed by Foa,[31] who is in agreement with the general opinion that alpha cells secrete a hyperglycemic-glycogenolytic factor. The almost invariable reduction in the beta to alpha cell ratio in our diabetics therefore raises the question as to what part the alpha cells play in the diabetic syndrome. Can a relative excess of alpha cells upset the hormonal balance of the islets? The subnormal total weights of alpha cells in the young and middle-aged suggests that under the age of 60 the influence of the alpha cells is usually not significant. Seven of the older patients (Cases 15, 16, 22, 24, 26, and 27; average age 67), however, possessed a bulk of alpha cell tissue roughly twice that of the control cases with comparable amounts of beta cell tissue (Cases 11, 13, 16, 22, and 29; average age 63) (figure 3). Two of these diabetics were obese, four received no regular insulin, and the others received respectively 5, 14, and 30 units daily. The diabetics with relatively high weights of alpha and beta cell tissue are, therefore, elderly, generally well nourished patients with a mild form of the disease. One cannot exclude the possibility that, in this group, a relative excess of alpha cells might influence the symptomatology of the disease.

Influence of Heredity

Although lesions such as pancreatitis and pancreatic carcinoma may cause diabetes, the disease is, as a rule, unassociated with gross destruction of the pancreatic parenchyma, and it has been suggested that the diabetic tendency is inherited as a simple recessive (Pincus and White,[32] Thompson and Watson,[33]). Obviously the abnormality transmitted in the inheritance of diabetes may concern either extrapancreatic organs, for example, pituitary or pancreas or both. Whatever the extrapancreatic diabetogenic influences involved, their effects might be expected to be more serious if the amount of beta cell tissue were already low.

In this connection the tendency to reduction in the size of the pancreas, particularly in the young diabetic, is of some importance. In the cases under review there was no evidence that old pancreatic necrosis or fibrosis, general bodily underdevelopment, or malnutrition could account for reduced weight of the pancreas. The pancreas of many diabetics, therefore, appears to be subject to some prenatal or postnatal developmental abnormality which may be hereditary. By incomplete development from ducts the islets might be similarly affected, thus rendering the subject unduly susceptible to diabetogenic influences. Indeed it is possible that, in childhood and adolescence, both pituitary hypersecretion and hypoplasia of pancreatic tissues may be concerned in the hereditary diabetic tendency.

"Latent" Diabetes

If our estimates are correct, it would appear that a substantial number of diabetic subjects over the age of sixty possess an amount of beta cell tissue near the lower limit of the values observed in the control group. Such patients may well continue in a low-grade diabetic state for a number of years before some complication or intercurrent febrile illness draws attention to the underlying metabolic disturbance. This is in accord with

clinical experience, since arterial, neurologic, and renal complications are often well established when diabetes is first diagnosed in elderly subjects.

CONCLUSIONS

The following findings in the group of diabetic cases investigated appear of considerable theoretical importance: (1) the tendency to hypoplasia in the diabetic pancreas which may render it unduly susceptible to diabetogenic influences; (2) the significant difference in quantities of pancreatic beta cell tissue in diabetics developing the disease before and after maturity, a difference which may largely account for differences in available insulin and hence in ketotic tendencies; and (3) the large islets and relatively high quantities of alpha- and beta-cell tissue found in many elderly diabetics. These findings are not incompatible with Young's[24] concept of the diabetogenic action of the pituitary, differences between young and elderly diabetics being governed by differences in susceptibility and by variations in intensity and duration of diabetogenic stimulation.

It must be emphasized that our results are drawn from a limited group of diabetics without hyalinization or significant fibrosis of the pancreatic islets; such obvious factors in the pathogenesis of the disease as hemachromatosis, pancreatic neoplasia, and acute, subacute, and chronic pancreatitis have not been considered. The group remaining, however, is substantial, and although the conclusions drawn from it are largely tentative and cannot be applied to the diabetic syndrome as a whole, its separation from cases displaying obvious causes and end results of the disease may, with further study, help to clarify the problem of the etiology of diabetes mellitus.

SUMMARY

1. Quantitative investigation of thirty diabetic pancreases with no hyalinization or significant fibrosis of the islets revealed, in the diabetic as compared with the nondiabetic pancreas, a tendency to reduction in the weight of the pancreas, the number of islets per pancreas, the proportion of islet tissue, and the proportion of beta cells in the pancreatic islets.

2. The last-mentioned factor affected diabetics at all ages, whereas the first three factors tended to affect most severely those who developed diabetes during the growing period.

3. Operation of these factors resulted in a significant reduction in the mean weights of islet tissue, alpha cells and beta cells as compared with control values.

4. The mean weight of beta cells in those patients developing diabetes in the growing period was very low, whereas in subjects developing diabetes after maturity it was about half that of the corresponding controls.

5. A tendency to an increase in the mean size of the islets with increasing age of the patient was seen in the diabetics but not in the nondiabetics.

6. The bearing of these findings on the etiology of human diabetes mellitus is discussed.

ACKNOWLEDGMENTS

It is a pleasure to acknowledge our indebtedness to Dr. Barnet Woolf for statistical advice on the methods employed in the investigation and for analysis of the results; to Professor G. L. Montgomery for kindly criticism of the paper; to our colleagues in the Department of Pathology for help in obtaining the pancreases; to Mr. John Mitchell for much of the histologic preparation; and to Mr. Clifford Shepley for the diagrams.

SUMMARIO IN INTERLINGUA

Estimation Quantitative del Texito del Insulas Pancreatic in Diabeticos

1. Esseva executate un investigation quantitative de 30 pancreases diabetic sin hyalinisation o significative fibrosis del insulas. In comparation con casos nondiabetic il esseva constatate que il existe in diabeticos un tendentia a reducer (1) le peso del pancreas, (2) le numero de insulas per pancreas, (3) le proportion del texito insular, e (4) le proportion de cellulas beta in le insulas pancreatic.

2. Le ultime del supra-mentionate quatro factores afficeva diabeticos de omne etates; le prime tres factores tendeva a afficer le plus severmente le patientes qui habeva disveloppate diabete durante le periodo de crescentia.

3. Le effecto de iste factores esseva un significative reduction del peso median de cellulas alpha e beta in le texito insular in comparation con valores de controlo.

4. Le peso median de cellulas beta in patientes qui disveloppava diabete durante le periodo de crescentia esseva multo basse; in patientes qui disveloppava diabete post attinger lor maturitate, ille peso esseva circa un medietate del valores observate in correspondente controlos.

5. Esseva observate in diabeticos, sed non in nondiabeticos, un tendentia del dimensiones median del insulas a augmentar se con le avanciamento del etate del patiente.

6. Es discutite le signification de iste constatationes pro le etiologia de diabete mellite in humanos.

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Diabetes and Head Injury

A Case in Court

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I believe that the following information in regard to a court action relating to a head injury followed by a diagnosis of diabetes may be of interest to the readers of the *Journal*.

A woman aged sixty-seven years sustained a head injury when she was entering a large food store. She claimed that a ladder which had been erected by an awning company to make certain adjustments in front of the store, fell against her forehead. She suffered a laceration about an inch and a half long. She was taken immediately to a local hospital where the wound was sutured; she was then sent home. That night she felt nauseated and vomited once. The family doctor examined her and advised that she return to the hospital because of the possibility of concussion of the brain or fracture of the skull. She was admitted to the same hospital the following day. A routine urinalysis showed the presence of sugar graded 4-plus; the fasting blood sugar was 389 mg. per 100 cc. A history of pre-existing diabetes was denied, but there was a history of hypertension present for some years prior to the accident with systolic readings as high as 190. During her stay in the hospital the blood pressure readings were between 170 and 190 systolic, 80 diastolic. The initial nausea and vomiting disappeared and there was no other complaint during her entire hospital stay of approximately three weeks. Her diabetes was controlled excellently with diet and insulin. A year and a half later, she had a cerebrovascular accident with residual right-sided hemiplegia.

The plaintiff sued the food store and the awning company for $100,000, alleging negligence on the part of the defendants resulting in injury to the head which she claimed caused immediate diabetes and the subsequent "stroke" one and a half years later. The trial held in the fall of 1954 in the United States District Court of the District of Columbia lasted two full weeks. The plaintiff was brought into the courtroom and presented to the jury on a stretcher. At the end of the first week, the defendants offered to settle the case for $10,000. The attorneys for the plaintiff rejected this offer.

I testified in court for the defendants. I stated that injury was not a cause of diabetes. Direct questioning lasted twenty minutes and the remaining time for a full day was occupied with cross-examination. The jury decided that the plaintiff suffered a blow on the head as a result of negligence on the part of the defendants and allowed $2,500 damage for this injury. The jury denied, however, that the blow on the head caused diabetes or caused the stroke and therefore did not allow monetary damages for these conditions.

The defendants claimed and presented ample and satisfactory medical evidence in testimony that injury was not a cause of diabetes. This verdict should be of considerable interest to those engaged in the clinical practice of medicine.

DISCUSSION

A number of workers recognize certain precipitating factors which may bring to light diabetes in an individual who might be considered a potential or latent, or undiagnosed case. In this category of precipitating factors are stress, trauma, obesity, and the therapeutic use of cortisone, hydrocortisone or corticotropin. However, a predisposition to diabetes must exist such as a family history, obesity, and similar conditions. Such a situation must not be confused with trauma per se as a possible immediate cause of diabetes.

The early literature, in the main prior to the discovery of insulin, and especially from foreign sources, is fairly abundant with case reports of diabetes which cite trauma as a causative factor. Even the early editions of Osler's *Principles and Practice of Medicine*[1] succinctly stated, "injury to, or disease of, the spinal cord or brain has been followed by diabetes." Later editions of Osler's text book revised by Christian[2] repeated that injuries to the brain and to the upper part of the spinal cord cause glycosuria, a somewhat modified view. However, Cecil[3] in the second edition of his text book on medicine published in 1930 stated "it is well known that injuries to the brain and extreme emotional disturbances produce in human beings a type of glycosuria which is usually transitory. There is, however, very meagre evidence that injuries to the nervous system produce true diabetes mellitus." Certainly the literature after the discovery of insulin and in particular of the past ten years casts grave doubt on the concept that trauma is a cause of diabetes.

Claude Bernard's famous piqûre experiments lent suggestive thinking to the concept that injury evokes glycosuria and possibly diabetes. Joslin and his co-workers[4] stated, "even the interpretation of the Claude Bernard puncture is questioned." Eisenhardt[5] noted "What is

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very significant is that in Dr. Cushing's own long experience in operating for tumors of the hypophysis or third ventricle, he found that such operations did not result in even a transient glycosuria." Horrax, in a personal communication to Joslin further said, "I can certainly confirm what Dr. Eisenhardt has told you regarding pituitary cases, both from my experience with Dr. Cushing's patients and from my own. Furthermore, I have been unable to find in my own records any instance of glycosuria in tumors of the fourth ventricle or fourth ventricle region." Monro[6] stated, "I can cite the fact that in over 3,000 craniocerebral injuries, I know of no case in which the trauma had produced either diabetes mellitus or glycosuria, by time the patients had left the hospital after treatment for their injuries."

Luntz[7] made a critical suggestion relative to the possibility of trauma provoking diabetes in wartime stating, "since it is probable that a number of men, once hostilities have ceased and their demobilization has been effected, may lay claim to compensation in cases in which diabetes develop in the course of time." Thomsen[8] after an exceedingly critical study doubted that trauma can cause diabetes. Thomsen based his opinion upon a very exhaustive review of cases in the Aarhus Hospital in Denmark between the years 1921 and 1935 and upon his own experimental investigations. Stern[9] reported a case of the development of diabetes three years after a serious injury, but there was a family history of diabetes. Direct trauma to the pancreas has an outside possibility of producing diabetes provided five-sixths of the pancreas or more of the islands of Langerhans are destroyed and rendered inactive by such a trauma. When we consider, however, the location of the pancreas and its protection by the heavy muscles of the back posteriorly and by other abdominal organs including the stomach, intestines, and liver anteriorly, one must conclude that any injury sufficient to damage it to the extent that enough islands of Langerhans are immobilized in function to cause diabetes, injury to the other organs would be so severe that death probably would ensue. Bowers[10] portrayed this aspect well and said that the pancreas is soft and movable and is seldom torn by traumatic force, unless the trauma is due to stabbing or to a missile. Usually when compressing forces injure the pancreas, the trauma to other important structures is multiple and so devastating that the patient cannot survive. When injury which was insufficient to warrant immediate medical attention occurs and claim was made at a later date that such injury caused diabetes, the assumption must be that the injury did not cause diabetes.

Admittedly, cerebral injuries as well as others may lead to glycosuria but this is temporary in character. Gissel[11] observed hyperglycemia in all head injuries resulting in unconsciousness the first three or four days after an injury. Undoubtedly the work of Houssay and Anderson[12] and Young and his workers,[13] which has shown the diabetogenic potentialities of the growth hormone of the anterior pituitary, has led to the erroneous deductions, by some, that skull injuries possibly affect the anterior pituitary gland to overproduction of the growth hormone and subsequent diabetes mellitus. Such thinking has not investigatively proven acceptable.

Joslin further confirmed his belief that trauma does not cause diabetes by very practical observation which I quote, "We have on record in this office the signed statement of a medical observer of pugilistic contests as follows: 'In my twenty-five years of experience in examining boys and men for both amateur and professional boxing throughout the United States, I have never come across one person who has ever had symptoms or any knowledge on their part submitted to me by them that they had diabetes or had been suffering from diabetes. In all the injuries due to trauma, I have never known one injury resulting from trauma that would in any way cause diabetes in any form or any symptoms which would pertain to that disease. During my years of experience, 90 per cent of the people who have participated in boxing exhibitions either in amateur or professional ranks have had repeated examinations and none has ever shown any signs or symptoms of diabetes in any of its forms." This is certainly a very practical presentation. Joslin made the very unequivocal statement that of the 40,000 patients who have consulted him for sugar in the urine, there has been no patient in which he believed trauma was the cause.

Sachar and associates[14] influenced by the studies of Cuthbertson[15] who called attention to large losses of nitrogen in patients after fractures, studied carbohydrate tolerance, blood ketone levels, and nitrogen balance after human fractures. They confirmed previous observations that there was an abnormal loss of nitrogen following trauma, a phenomenon usually referred to as the catabolic phase and noted changes in sugar tolerance varying in degree and time of response. In half of their cases the sugar tolerance change was so marked as to place the patient in a "diabetic" group. In a third of the cases the loss of tolerance was negligible or absent. In all the sugar tolerance gradually improved as the nitrogen balance again improved. They concluded that the "post traumatic diabetes" is self limited and temporary.

Associated of course with trauma in the minds of many, have been emotional and nervous disturbances giving rise to what is commonly called neurogenic diabetes. Joslin rapidly disposed of this concept by quoting von Noorden, who well said neurogenic diabetes, "was put into the grave by World War I, and there it is likely to remain, no data yet appearing to show that it was exhumed during the recent conflict (World War II)." Certainly, the experiences of both World War I and World War II, should confirm the opinion that trauma or emotional disturbances do not cause diabetes. It is interesting to note that in Germany diabetes in the army was less frequent than in the civilian population. Joslin stated that as a medical consultant in a center through which over 38,000 soldiers passed and of whom over 12,000 were classified as battle casualties, only two cases of diabetes were reported. We ordinarily think the incidence of diabetes in the civilian population is 0.5 to 1.5 per cent. Joslin's observation is markedly below the percentage of diabetics in the civilian population and we would normally expect, at least, as great a percentage, if not greater, if trauma and emotional disturbances were considered causative factors.

Menninger[16] and Daniels[17] have both expressed the opinion that not only is there a correlation between mental stress and strain and increase in the severity of an already established diabetic state but that diabetes may be initiated by psychological or emotional disturbances. Menninger, however, laid down such rigid requirements which I shall discuss later, that I would be willing to accede to the concept under these conditions. Matz[18] studied diabetes in veterans of World War I and came to the conclusion that neurogenic factors are of no importance in the etiology of diabetes. Gendel and Benjamin[19] made an exhaustive study and review of forty-four cases admitted to the medical service of the Lovell General Hospital during their army service and came to the conclusion that "in no case was it possible to prove a direct cause or relation between the stress incident to military service and the subsequent development of permanent diabetes."

A thorough review of the medical literature for the past twelve years has revealed only three reports citing trauma as a cause of diabetes. These appeared in French publications. One must keep in mind that many countries have accident insurance and that a liberal interpretation of insurance benefits has come to be expected. American literature during the same period does not cite any cases giving trauma as a cause of diabetes.

After a careful and considerate review of the subject, I am definitely and unequivocally of the opinion that neither trauma nor emotional disturbances are etiological factors in producing permanent diabetes.

CRITERIA WHICH MIGHT JUSTIFY A DIAGNOSIS OF PERMANENT DIABETES MELLITUS DUE TO INJURY OR EMOTIONAL DISTURBANCES

For those who might still believe that trauma can cause diabetes, I would set forth the following criteria which might justify a diagnosis of diabetes due to injury:

1. There shall be nothing in the history prior to the accident pointing to either evident diabetes, latent diabetes, or a predisposition to diabetes. Those who have a family history of diabetes and in whom trauma has been considered as a possible cause should be ruled out.[20] Likewise, I would consider a person who is thirty pounds overweight as predisposed to diabetes and such a case should be ruled out.[20]

2. The first signs of diabetes must follow soon after the trauma. Personally, I would consider one month as the limit although Jacobi and Meythaler[21] consider a year as the longest interval permissible. According to the observations of Sachar and his associates[14] six to eight weeks would be a justifiable interval.

3. Conclusive evidence that diabetes did not exist prior to the trauma must be presented. This evidence must show the absence of glycosuria, the absence of hyperglycemia, and the absence of a diabetic glucose tolerance curve.

4. The existence of true diabetes after the trauma must be established with certainty as evidenced by positive tests mentioned previously. The demonstration of transient glycosuria is insufficient evidence.

5. Evidence must be presented that trauma was severe, injuring the pancreas.

Menninger[16] sets forth high requirements to which psychogenically induced permanent diabetes should conform. These are as follows:

1. An obvious psychopathic state evidenced prior to the development of diabetes.

2. A mental picture quite different from the toxic state occasionally seen in hyperglycemia or hypoglycemia.

3. A course of improvement in the mental picture paralleled by the glycemic and glycosuria levels, with fluctuations of these as emotional upsets occur in the psychic life.

4. Indication of the metabolic disorder by a persistent glycosuria, without dietary control or insulin, retarded glucose-utilization curves of the blood sugar and a response to dietary and in some cases insulin therapy.

5. Clearing of the diabetes on mental recovery without the necessity of insulin or rigid dietary treatment.

Even admitting and accepting Menninger's criteria, a diagnosis of diabetes under these circumstances would be debatable, and one might argue that it could be called a temporary disturbance of carbohydrate metabolism and not true permanent diabetes.

SUMMARY AND CONCLUSION

A case report is submitted in which an injury to the head was alleged to have caused permanent diabetes mellitus and a subsequent cerebral vascular accident. Testimony and data submitted caused the Court to hold that neither the diabetes mellitus nor the subsequent vascular accident resulting in hemiplegia was the result of the injury.

A discussion with a review of the literature concerning the relationship of physical trauma and emotional disturbances as a cause of diabetes is presented, together with certain criteria which might justify a diagnosis of diabetes being made as a result of these factors.

It is the opinion of the author that there is insufficient evidence in the medical literature to justify a conclusion that physical trauma and/or psychogenic factors can cause permanent diabetes.

SUMMARIO E CONCLUSION IN INTERLINGUA

Diabete e Vulneration del Capite: Un Caso de Litigio

Es presentate le reporto de un caso in que le allegation esseva facite que un vulneration del capite habeva causate permanente diabete mellite e un subsequente accidente cerebrovascular. Datos e testimonios ponite al disposition del tribunal duceva al verdicto que ni le diabete mellite ni le subsequente accidente cerebrovascular resultante in hemiplegia esseva causate per le vulnere.

Es discutite le question de trauma physic e de disturbation emotional como causa de diabete. Le litteratura pertinente es revidite, e certe criterios es presentate que poterea possibilemente justificar le diagnose de un caso de diabete como resultato de tal factores traumatic e emotional.

Le autor opina que le litteratura medical non offere un sufficiente grado de evidentia pro justificar le conclusion que trauma physic e/o factores psychogenic pote causar permanente diabete.

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The Natural History and Identification of Diabetes

Panel Discussion

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Moderator

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Blair Holcomb, M.D.§
Portland, Oregon
*Henry T. Ricketts, M.D.***
Chicago
Garfield G. Duncan, M.D.‡
Philadelphia
Francis D. W. Lukens, M.D.‖
Philadelphia
Howard F. Root, M.D.††
Boston

MODERATOR MULHOLLAND: Dr. Colwell, I believe you have made the statement in a published article that diabetes is a syndrome and not a disease. Will you explain what you mean by that term?

DR. COLWELL: From my viewpoint, Dr. Mulholland, diabetes mellitus is not a disease. It is a syndrome, characterized by relatively persistent hyperglycemia and glycosuria when untreated. In the majority of cases the cause cannot be determined or removed, but, like fever, hypertension, and tachycardia, for example, the syndrome can be due to a variety of causes, some of which can be determined and a few removed. Our habit of thinking of diabetes as a disease entity stems from the fact that in the ordinary case a cause cannot be assigned. There is good reason to believe that it is inherited like idiopathic epilepsy and migraine; however, the exact mechanism is unknown. Even so, the clinical features of this common form are indistinguishable from those less common cases which are caused by acromegaly, hypercorticoidism, pheochromocytoma, and loss of pancreatic function. Persistent hyperglycemia and glycosuria can also be caused by administration of certain hormones and drugs. It can even accompany emotional stress and hepatic disease. These syndromes must also be called diabetes by my definition.

By such criteria the treatment varies accordingly in that when a cause can be found and removed, that should be done in addition to the therapeutic methods ordinarily used.

MODERATOR MULHOLLAND: Does any other member of the panel have comments to make about Dr. Colwell's statement? Dr. Ricketts?

DR. RICKETTS: I would like to ask Dr. Colwell if he would regard the presence of glycosuria necessary. I believe his definition implied this. Would not hyperglycemia with high renal threshold be diabetes?

DR. COLWELL: Yes, I agree that persistent hyperglycemia without abnormal glycosuria should also be considered to be diabetes and treated as such.

MODERATOR MULHOLLAND: Does everyone else on the panel agree with Dr. Colwell's definition? Dr. Root, you are smiling. I don't know whether you are going to consent to it.

DR. ROOT: I think Dr. Colwell as a medical teacher will agree that the tendency during the last one hundred

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years is more and more to define clinical entities as accurately as possible. I disagree with the definition of diabetes mellitus as a syndrome because I think diabetes is basically an hereditary disease. When we say diabetes, we do not mean hyperglycemia alone; we mean a clinical disease which in given families carries with it the capacity for transmitting from one generation to another this tendency to develop diabetes under various kinds of stress. I prefer to believe that in the last fifty years the tendency has been to limit the use of the words "diabetes mellitus" to this chronic hereditary disease and to get away from using terms such as "hepatic diabetes" and "fasting diabetes." Indeed the term "fasting diabetes" is a complete error since there is no such thing as diabetes mellitus produced by fasting. It is actually a hyperglycemic response with glycosuria in a patient who has been subjected to the stress of starvation. I should like to use the word "diabetes" then only in connection with true diabetes mellitus.

DR. COLWELL: Then what would you call the hyperglycemic condition associated with pheochromocytoma and cured by its removal, Dr. Root?

DR. ROOT: If there is no hereditary element present, the hyperglycemia and glycosuria are due to pheochromocytoma and nothing else. I should say that it is hyperglycemia and glycosuria due to pheochromocytoma.

DR. COLWELL: I suppose it is a matter of semantics. I think it is easier to use one word instead of two and call it diabetes.

DR. ROOT: If it is permanently removed by that operation, then I don't think it was diabetes.

DR. COLWELL: Certainly the ordinary garden variety will not disappear, I agree.

MODERATOR MULHOLLAND: Any other comments from the panel? Dr. Root, you spoke about an hereditary tendency. Do you think all diabetes must be hereditary?

DR. ROOT: All the diabetes that I know about has an hereditary background.

MODERATOR MULHOLLAND: Can you prove that?

DR. ROOT: No, I cannot prove it conclusively. However, the longer diabetic patients are observed, the greater is found to be the frequency of diabetes in the relatives. In the symposium on experimental diabetes and its relation to the clinical disease organized by the Council for International Organizations of Medical Sciences (published in 1954 by Charles C Thomas) it is stated by P. Hanssen that recent investigations have completely confirmed Naunyn's view on the vital importance of heredity in the pathogenesis of early cases of diabetes. Of those the special conditions under which the disease is transmitted are uncertain. He quoted the conclusions of Harris that diabetes is not a single genetic entity. Thus cases of diabetes beginning in young persons and cases beginning late in life may have their origin in different combinations of genes. Upon this genetic background other factors may be superimposed.

DR. COLWELL: I am sure that Dr. John Howard of Baltimore thought his patient had diabetes for about two years, as I recall, before the removal of a pheochromocytoma brought about its disappearance.

DR. ROOT: Yes, I'm sure he did. The symptoms, hyperglycemia and glycosuria, are not sufficient as a definition of diabetes. Surgical removal of a pheochromocytoma would cure these symptoms unless the patient had also underlying true diabetes. I am sorry to have these people confuse the term "diabetic state" with the clinical disease that we know as diabetes mellitus.

DR. HOLCOMB: I'd like to ask Dr. Colwell to explain alimentary glycosuria.

DR. COLWELL: Alimentary glycosuria is an ill defined phenomenon, I think. A wave of hyperglycemia and glycosuria following large carbohydrate feedings should be considered to be diabetic until proved otherwise. A notable exception is its frequent appearance in persons with rapid emptying of the stomach after partial gastrectomy or gastroenterostomy. I have frequently seen glycosuria and blood sugar peaks as high as 360 mg. in such persons. Normal and even subnormal blood sugar levels are reached an hour or two later. A diabetic person should not show this, and the subsequent history in such cases proves the absence of diabetes. In other words, the hyperglycemia in such cases does not persist so that the behavior is not diabetic. It is a fairly common feature of the "dumping syndrome."

Do you agree with this definition, Dr. Holcomb?

DR. HOLCOMB: Yes, I should think so. I should like to ask another question. Do you think that the appearance of glycosuria and hyperglycemia after the administration of desiccated thyroid to an individual who has presumably had a normal carbohydrate tolerance indicates diabetes? In such a case do you think there must be a tendency to diabetes which is simply activated by the use of thyroid?

DR. COLWELL: No, I would not judge this to be inherent diabetes but a transient diabetic syndrome due directly to thyroid administration. Various substances including desiccated thyroid can cause hyperglycemia and glycosuria in normal persons persisting until their administration has been stopped.

DR. HOLCOMB: Suppose that an individual never shows glycosuria or hyperglycemia on a normal diet but does have transitory glycosuria and hyperglycemia after overeating at a banquet or after eating a lot of candy. Would you say that he has diabetes?

DR. COLWELL: Yes, I should think that if it occurred regularly he would have to be considered diabetic by definition.

DR. HOLCOMB: I should like to ask Dr. Duncan what he considers a diabetic glucose tolerance curve.

DR. DUNCAN: I consider an abnormal glucose tolerance curve one in which the blood sugar is not normal in two hours, provided the patient has been properly prepared for the test (assuming that there has been 300 gm. of carbohydrate in the daily diet at least three days in advance) and that complications such as infection, pregnancy, and thyrotoxicosis can be excluded.

I should like to add a word to Dr. Colwell's answer about the thyrotoxic patient. I wonder if hyperglycemia can be explained as in the dumping syndrome by an increased speed of absorption. An intravenous glucose tolerance test yields what we consider a normal type of curve even though the alimentary glucose tolerance test might be interpreted as being indicative of diabetes.

MODERATOR MULHOLLAND: Dr. Duncan, you spoke of the proper preparation for a glucose tolerance test, emphasizing the need for a high carbohydrate diet for at least three days in advance. I have seen a recent criticism of this recommendation. It has been claimed that no more than 100 gm. of carbohydrate daily are needed. Do you believe that?

DR. DUNCAN: I have had no experience with that modification of the glucose tolerance test. I should expect a reduced carbohydrate intake to result in elevation of the curve obtained in the glucose tolerance test.

MODERATOR MULHOLLAND: Dr. Ricketts?

DR. RICKETTS: This has been investigated, and as I remember the results, the line of demarcation between adequate and inadequate preparation for a glucose tolerance test in terms of carbohydrate intake lies somewhere between 50 and 125 gm. per day. Above these levels you are quite sure of getting a normal curve in a normal individual. Below these levels you are quite sure of getting a diabetic curve and somewhere between, the results may be equivocal.

MODERATOR MULHOLLAND: Do you agree with this criticism or do you agree with Dr. Duncan?

DR. RICKETTS: I do what Dr. Duncan does to be safe.

MODERATOR MULHOLLAND: Do the members of the audience have any questions at this point?

QUESTIONER: I would like to ask Dr. Duncan what type of blood sugar examination he employs. He spoke of a blood sugar value of 120 two hours after glucose.

DR. DUNCAN: I was referring to a venous blood sugar determination by the Folin-Wu method. Normally the blood sugar by this method is 120 or less two hours after the 100 gm. of glucose given the usual adult patient.

MODERATOR MULHOLLAND: It has been stated that different species of animals show considerable difference in the way they react to removal of the pancreas. Dr. Ricketts, do you think that a depancreatized human being is a true example of a case of diabetes mellitus?

DR. RICKETTS: I think that he is, Dr. Mulholland, in every respect that I can think of.

MODERATOR MULHOLLAND: Is it a fact that the diabetes is generally mild with requirement of only a small amount of insulin?

DR. RICKETTS: Yes, it is true that in none of these cases is the usual insulin requirement more than 40 to 50 units. I should say, of course, that since the external secretion of the pancreas is obviously lacking they certainly differ from patients with spontaneous diabetes in this respect. But in respect to their ability to get along without insulin the diabetes is just as severe as in any case of spontaneous diabetes. It seems that with the single exception of the small insulin requirement there is very little difference between artificially produced diabetes and the naturally occurring diabetes in man.

DR. ROOT: Dr. Ricketts, I understand that there have been cases in which the diabetes following complete pancreatectomy could not be controlled with 30 to 40 units of insulin and that the insulin requirement had risen to at least 80 units.

DR. RICKETTS: This matter was reviewed recently in a short editorial in the Journal DIABETES. My attention was called to it by Dr. Frank Allan. There have appeared in the literature two or three accounts of totally depancreatized human beings whose insulin requirement on occasion would rise above the 40 or 50 unit level. These occasions represented periods of stress, and it is no surprise to me to learn that a period of stress in a depancreatized man will cause an increased requirement for insulin just as it may in a depancreatized animal. What we were talking about in our earlier conversation was the habitual state of the depancreatized man; under these circumstances my first remark is still true.

DR. COLWELL: Mr. Chairman, to revive our previous dispute, I should like to ask Dr. Root if he would call this "pancreatectomy diabetes" or "pancreatectomy hy-

perglycemia and glycosuria."

DR. ROOT: I think the hyperglycemia thus produced is due to hypoinsulinism and not due to diabetes mellitus. I think the condition shows little resemblance to clinical diabetes mellitus as we see it among patients we treat.

DR. COLWELL: How is it different?

DR. ROOT: The patients we see with diabetes mellitus have an hereditary condition with pancreatic inferiority where the person who has only suffered pancreatectomy does not have an hereditary diabetic tendency. By the operative removal of the pancreas you do not produce diabetes mellitus but merely hypoinsulinism. You have not conferred upon that person the capacity for transmitting any hereditary tendency into the next generation.

DR. COLWELL: We can be in complete agreement if you want to call the idiopathic or perhaps hereditary condition "diabetes mellitus" and other varieties "diabetic states or syndromes."

DR. DUNCAN: I wonder if we shouldn't look upon a pancreatectomy type of diabetes as experimental diabetes, as being quite different from clinical diabetes in which we use hyperglycemia and glycosuria as the criteria to make the diagnosis. Certainly we see patients with evidence of clinical diabetes long before these criteria appear, such as the birth of a big baby, the mother of whom does not develop the diabetes which we predict until probably five or ten years later. Occasionally we see typical diabetic retinitis or diabetic neuropathy, and if diabetes exists in the family we predict that probably this patient will develop diabetes later. I am just wondering if there is not an underlying process influenced by the genes, let us say, which goes along and eventually destroys the efficiency of the pancreas, and eventually hyperglycemia and glycosuria occur. Hemochromatosis is another type of disorder which eventually causes a form of diabetes. Ordinarily clinical diabetes is quite different from the diabetes caused by pancreatectomy.

MODERATOR MULHOLLAND: That is an interesting observation. I think Dr. Root might give you some support on that.

QUESTIONER: Given an intact circulation, is there any difference in the utilization or in the effect of insulin when given intravenously or hypodermically?

DR. DUNCAN: For a great number of years I taught students not to depend on insulin given intravenously. Dr. Barclay Biedleman when he was with us tested the administration of insulin intravenously and subcutaneously and invariably it is more effective more promptly when given intravenously than when given subcutaneously, but I am not at all sure that that proves that it would act in the same way in the presence of ketosis or sepsis. I avoid the intravenous administration of insulin except in the case of the initial dose in the treatment of diabetic coma when I want that chance of a very rapid action, or when poor absorption might be present as occurs in peripheral vascular collapse.

MODERATOR MULHOLLAND: Dr. Lukens, perhaps you can contribute to these discussions.

DR. LUKENS: I should like to make one comment in connection with the discussion of pancreatectomy in man. For the very obvious reason that it is difficult, physicians have not applied to the depancreatized man the standard criteria set up by Minkowski in 1889. If we would measure the excretion of glucose and nitrogen during fasting as Dr. Ricketts tried to do to the best of his ability, we would then see quite clearly that pancreatectomy in man is the most severe form of diabetes with which we have ever come in contact. Dr. Ricketts stated that this was so and I wish to echo it. I think it is very important to realize that the severity of diabetes is measured by multiple criteria. What is the severity of the mildest type of diabetes? It is an abnormal glucose tolerance test, and there may be little or no glycosuria. What is the severity of the moderately severe case of diabetes? It is likely to be in the proportion of the available glucose in the diet excreted in the urine. Then you go up to severe diabetes, and the fasting glucose and nitrogen excretion are your best measurements. It is very difficult for those of us who live in one room to be fully cognizant of what is going on in the next room.

MODERATOR MULHOLLAND: Thank you, Dr. Lukens. I see that another member of the audience would like to ask a question.

QUESTIONER: Dr. Duncan, what happens to the blood sugar in shock?

DR. DUNCAN: I'm not sure what kind of shock you are referring to—if it is the kind a woman receives in a telephone message that her husband has been shot, or if it is the type which occurs in myocardial infarction. Ordinarily there is an increase in the blood sugar for a short period. I suppose that the effect is similar to the injection of epinephrine.

MODERATOR MULHOLLAND: Is that the kind of shock you have in mind—surgical shock?

QUESTIONER: Yes, sir, surgical shock.

MODERATOR MULHOLLAND: Would anyone else wish to comment on this?

DR. COLWELL: Yes, I think it is generally agreed

that there is hyperglycemia during shock. In fact, in any condition in which there is diminished blood supply to the liver with anoxia, there is an increased glucose supply and hyperglycemia, assuming the presence of adequate glycogen.

QUESTIONER: I should like to ask Dr. Root if he agrees with Dr. Duncan that the peak of glucose tolerance tests has little diagnostic significance.

DR. ROOT: I once thought that peaks in a glucose tolerance test were of little diagnostic value. Then in Vienna I encountered in a medical journal a description of a remarkable child. The child was described as having hepatic diabetes because after glucose had been discovered in the urine the glucose tolerance test was made. The blood sugar rose to 400 mg. per 100 cc. at the peak, but at the end of two hours the blood sugar had returned to normal. This case was reported as an extraordinary case of a child with a liver disorder. Some nine months later the doctor who had reported the case arrived in Boston and the first thing he said to me was, "Dr. Root, I am sorry to have to tell you that there was an error in that case report. Only a few months later that child had true diabetes mellitus and is now taking insulin." At present Dr. Hugh Wilkerson is conducting an investigation of pregnancy in diabetic women. He and his group of advisors which includes Dr. Lukens and Dr. Ricketts are applying a standard which makes use of both the peak and the two hour value in interpreting the glucose tolerance test in a large series of pregnancies. Their results will be awaited with great interest.

In our own series of cases I can say that as we follow patients over the years we find that many who have had a single hour blood sugar value exceeding 170 mg. have shown the development of true diabetes mellitus with classical symptoms in the course of a ten-year period. We have therefore come to regard a high peak in a glucose tolerance curve (exceeding 170, using venous blood in the Folin-Wu method), as not perhaps proving diabetes but at least indicating that the patient has an abnormality and that he needs repeated follow-up examinations for life.

DR. HOLCOMB: I should like to present this question. A diabetic patient is treated with diet and insulin for a period of one year. During this time his weight is reduced forty pounds to a normal figure. Treatment with insulin is discontinued. In a few months he is able to take a diet with a liberal amount of carbohydrate without glycosuria or hyperglycemia. A glucose tolerance test at the end of one year is normal. Three years later under stress, hyperglycemia and glycosuria return and treatment with insulin is again needed. A situation like this makes me wonder if a glucose tolerance test is a sufficiently sensitive method of detecting diabetes of very mild degree.

MODERATOR MULHOLLAND: That is a good question. Do you wish to answer it, Dr. Lukens?

DR. LUKENS: I have said for some time that an infection with fever brings about more stress than 100 gm. of glucose. This is illustrated by your case.

Fajans and Conn have attempted to make the glucose tolerance test more sensitive by administering cortisone in advance of the glucose. Among the relatives of diabetics a fairly high incidence of positive tests was found with this technic. Further efforts to use more sensitive tests may be made in this direction.

DR. HOLCOMB: What do you think about the obese diabetics who have been shown to have a normal glucose tolerance test after weight reduction?

DR. LUKENS: If they were once diabetic I think that diabetes is still present as in the case that you cited.

DR. RICKETTS: I can answer that question of Dr. Holcomb's a little more specifically. Dr. Conn told me that not long ago when he followed up these cases which he and Dr. Newburgh originally reported, I think more than fifteen years ago, he found that a good many who had apparently lost their diabetes after reduction of excess weight had subsequent development of true diabetes mellitus. This substantiates Dr. Lukens' guess on the subject.

MODERATOR MULHOLLAND: All of us are interested in the fact that diabetics generally have a high incidence of vascular disease of all types. Dr. Ricketts, do you believe that vascular disease is part and parcel of the natural history of diabetes?

DR. RICKETTS: It seems to me we have to say it is, in the vast majority of cases. One of the most informative studies I know of on the subject was undertaken by Dr. Root and I think he ought to talk about it instead of me. I merely want to say that in the experience of Dr. Root and his colleagues there was high incidence of retinopathy and nephropathy in cases of long-term diabetes, and in most of these cases the diabetes had been poorly controlled. There were however a few cases of severe diabetes in which these complications did not develop in spite of poor control. On the contrary, these complications were absent in most of the cases of mild diabetes generally well controlled, but they did occur in a few such cases. All of this adds up in my way of thinking to the statement that most of the vascular degeneration occurring in diabetes is seen in cases in which the disease has been

present for a long time and with glycosuria poorly controlled. There are a few exceptions, and these exceptions form almost the most intriguing part of the problem.

MODERATOR MULHOLLAND: Dr. Root, do you wish to say something about this question? You have been interested in it for many years.

DR. ROOT: In our study of some 450 cases of diabetes selected because of onset of the diabetes early in life before the age of twenty-five years, we made use of X-ray examination of the arteries in the legs, the aorta, and the pelvic vessels, examinations of the eye grounds, and tests of the urine and blood for evidence of kidney complications. We classified these cases according to the type of control of diabetes over the period of ten to twenty years. Actually the percentage of patients in the group labeled as having been in "poor control," (that is, with hyperglycemia, glycosuria, and only occasional medical examinations) and who developed serious lesions in the arteries in the eyes was very high. The percentage of those who escaped lesions in this group at the end of twenty years was very low. On the other hand among patients who had been kept under very good control, a large majority escaped any of the severe retinal and renal complications. Indeed, none in the group of "good control" had developed the typical diabetic nephropathy. Unfortunately, there is still a group of physicians—some of them opthalmologists—who quote statements to the effect that there is no relation between the severity of diabetes and the retinitis of diabetes. In our group of patients the facts are exactly reversed. We have now studied nearly 500 cases of retinitis proliferans, and it is obvious that the frequency of retinitis proliferans of the malignant sort is many times greater in severe diabetes which begins early in life as contrasted with the mild diabetes which begins late in life. There is in our group a very direct relationship between the severity of diabetes and the severity of the eye lesions.

DR. HOLCOMB: I have a suspicion that the development of vascular complications in cases of diabetes may be related in part to an inherited susceptibility to cardiovascular defects.

QUESTIONER: I am wondering if exercise may be a factor in the cases in which there is freedom from the development of arteriosclerosis.

DR. COLWELL: I don't have any reason for thinking that exercise might prevent vascular disease in diabetes. All we can do is speculate about the cause. Certainly vascular disease is a most intriguing and important question about which the evidence is just beginning to accumulate.

DR. DUNCAN: In regard to the question about exercise, I am not entirely in accord with Dr. Colwell. I believe that exercise has a rather definite effect and that those who earn their living through muscular activity are less likely to develop diabetes than those with sedentary occupations.

Changing the subject, I am wondering if we haven't been feeding our diabetic patients too much fat in view of Dr. Ancel Keys' observations. Should we not raise the carbohydrate, provided it doesn't increase the difficulty in controlling the diabetes? I have given more and more carbohydrate up to the limit or a little short of it, where it might cause difficulty in controlling the diabetes. I wonder if Dr. Root would like to comment on these points—the amount of fat in the diet, and exercise.

DR. ROOT: I quite agree. Certainly our practice in recent years has been to give more carbohydrate and less fat in the dietary prescription. We rarely prescribe over 250 gm. of carbohydrate per day, and indeed our prescriptions are more nearly in the area of 150 to 200 gm. per day. My experience has been that if you try to force diabetic patients to take 300 to 400 gm. of carbohydrate by the addition of syrup and sugar, the diabetes is not merely more difficult to control but there may also be a tendency for conversion of what was at first relatively mild diabetes into more severe diabetes.

MODERATOR MULHOLLAND: There are some disagreements—I see that some of the members of the panel are shaking their heads.

DR. DUNCAN: We give more carbohydrate than does Dr. Root, and we draw the line where there is difficulty in controlling the diabetes. I have been very much impressed with Keys' surveys of the amount of fat in the diets of various groups, and I wonder if more fat can be tolerated by individuals who have a great deal of exercise. The possible favorable effect of exercise in relation to the development of vascular disease, it seems to me, has been largely overlooked in the investigations in this field.

DR. HOLCOMB: We began using diets relatively high in carbohydrate and low in fat in 1926, but the amount of carbohydrate prescribed varies considerably. Some patients cannot take more than 150 gm. of carbohydrate a day. They don't want more than that. On the other hand the lean laborer may need 330 gm. of carbohydrate, 150 gm. of fat, and 160 gm. of protein to maintain his weight. Thus the amount of carbohydrate, protein, and fat should depend on the individual

and his activities.

When we find that a patient has difficulty in controlling his diabetes despite fidelity to his diet, we have recently gone back to the old practice of using 100 gm. of carbohydrate, raising the fat to keep the diet isocaloric. Thus we have kept the diabetes under good control, and tolerance has been regained. Diabetes may be much more stable with such a diet than when a high carbohydrate diet is used.

DR. COLWELL: I should like to present the other side of the question. My custom has been to be less liberal with carbohydrate than this. My reasons have been three: First, I have yet to be persuaded that high fat diets can cause atherosclerosis. Second, even though blood cholesterol levels are a factor, good control of the diabetes is more important than the amount of fat in the diet in encouraging normal blood lipid levels. Finally, it is much easier to control abnormally high blood and urine sugar in diabetes when the carbohydrate eaten is moderate in amount. Like many others, I believe that we should maintain normal levels as well as possible in an effort to avoid vascular complications unless and until it is proved that it is unnecessary. For these reasons I prefer not to be extravagant with carbohydrate.

MODERATOR MULHOLLAND: Some believe that the vascular lesions in the eyes and in the kidneys are peculiar to diabetes. Are they different from vascular lesions in nondiabetics, Dr. Ricketts?

DR. RICKETTS: The fact is that in both the retina and the kidney the lesions which we regard as characteristic of diabetes have been described in nondiabetic states, but only under rare circumstances. Certainly the overwhelming number of such lesions found by the pathologist and the ophthalmologist occur in cases of diabetes and particularly in cases of diabetes of long duration.

Becker and Friedenwald in post-mortem studies have found that patients with diabetic retinopathy have shown in practically all instances the presence of the Kimmelsteil-Wilson type of lesion in the kidneys. The association between these lesions in the two parts of the body seems to be very close indeed.

MODERATOR MULHOLLAND: What do you think about the relationship between the development of these lesions and function of the adrenals, the metabolism of vitamin B_{12} and pantothenic acid? I have heard a good deal about these factors in recent years.

DR. RICKETTS: I don't know what to think, Mr. Chairman. It is too early for me to say.

MODERATOR MULHOLLAND: Do you think that this problem is entirely in the experimental stage?

DR. RICKETTS: Yes, sir.

MODERATOR MULHOLLAND: Can you express an opinion about the significance of these factors?

DR. RICKETTS: No, except to cite what facts are known. The facts are that two different groups (in Baltimore and in Columbus, Ohio) have succeeded in producing both renal and retinal lesions in diabetic rabbits by the use of cortisone and/or corticotropin. This has been confirmed and probably has some significance. What that significance is for man I can't say at this point.

Perhaps Dr. Lukens would like to comment about his pituitary diabetic dog which apparently developed Kimmelsteil-Wilson lesions.

DR. LUKENS: That was a single animal—it was an odd occurrence. It suggests the possibility that in the next few years these lesions may perhaps be studied in the laboratory.

Far more important observations have come from South America on the one hand and from Boston on the other. Rats made diabetic have developed a high percentage of renal lesions in as short a time as two or three months. These rats were untreated. Any form of treatment or absence of diabetes appeared to prevent the lesions.

Our hopes for laboratory investigation of this problem must be guarded since it may take ten to twenty years for these lesions to develop in man. It is quite clear that the laboratory worker is going to take a long time to solve the problem.

DR. RICKETTS: Dr. Lukens, are you convinced that these experimental lesions in the rats are reasonably identical to the lesions occurring in man?

DR. LUKENS: I cannot answer the question about the identity in the case of the rat. In the case of the dog, we thought it was close enough to make the suggestion.

DR. RICKETTS: I agree with you about the dog.

DR. LUKENS: I do think this. These lesions whether they are identical or not are the result of diabetes in the rat; that seems to be fairly clear, and with that little bit of a stepping stone we might move on.

DR. RICKETTS: Unless they are the result of alloxan.

DR. LUKENS: No, because four years of experiments with partial pancreatectomy eliminate that.

DR. COLWELL: Yes, alloxanized animals which do not become diabetic do not develop the lesions.

MODERATOR MULHOLLAND: A question has been asked in regard to the basic difference between juvenile and adult diabetes mellitus.

DR. RICKETTS: I will start if you like. It seems to me Wrenshall made a most notable contribution to this problem by showing that diabetes beginning in childhood is accompanied by the almost total absence of extractable insulin in the pancreas. However, diabetes beginning in adulthood is characterized in some cases by a marked diminution of insulin, in other cases by very little diminution, and on the average by about 50 per cent of the insulin content of the normal pancreas. For the want of a better explanation for the unstable and labile behavior of the juvenile diabetic, my thinking is now running along this line. This individual is totally dependent on injected insulin. There is no injectable insulin which has the homeostatic control over the blood sugar that a normal pancreas has. There is no preparation of insulin put under the skin which can close down its insulin output when the demand decreases and increase that output when food is taken or when stress is experienced. It seems to me that with the information we have available this is the best explanation for the instability of the juvenile diabetic, and if one follows that line of reasoning it is easier to see why the adult diabetic who has some pancreatic reserve left, some ability to vary his insulin secretion with the coming and going of need, is better able to achieve a reasonable degree of homeostasis.

DR. COLWELL: It should be added that when diabetes begins in the first two decades of life, almost always it becomes severe very rapidly. Rarely is there any exception to the rule that it progresses into a severe form totally dependent upon insulin for life. By all criteria this is total diabetes—the most severe form seen in humans. In older people severe diabetes such as this is less common, but when it does occur in my experience those people tend to be thin and diabetes has been present a long time. Older people are more often fat, however, and have milder, less rapidly progressive forms of the disease. Clinical experience suggests that the diabetes now thought by physiologists to be an insulin-deficient variety is the kind present in most juveniles, whereas in the older people with milder forms of the disease the mechanism may be quite different. Certainly they are less dependent upon insulin as a rule.

QUESTIONER: In performing an autopsy on a twenty-six-year-old man who had had diabetes for twenty years, I noted marked sclerosis of the coronary arteries and typical Kimmelsteil-Wilson changes in the kidneys. The major arteries, however, showed no change. How can this be explained?

DR. ROOT: The number of young diabetic patients who begin to show clinical evidence of coronary artery disease in the early twenties is certainly increasing. We have seen a good many cases in which the amount of coronary atherosclerosis was advanced far beyond any change noted in the aorta or other arteries. In most cases, coming to post-mortem between the ages of twenty and forty with a history of diabetes for twelve to fifteen years there is not only coronary atherosclerosis but a good deal of atherosclerosis in the other arteries as well.

DR. HOLCOMB: I have recently seen a boy of fifteen with diabetes of two months' duration who died in coma; at the post-mortem examination atherosclerosis was found in the coronary arteries and in the aorta.

MODERATOR MULHOLLAND: Have patients with total pancreatectomy been followed long enough for observation of the development of vascular lesions as seen in cases of idiopathic diabetes? Does anyone know of such a case or cases?

DR. RICKETTS: This is a very good question. I don't know of any such cases. This much I can say. Dr. Lawrence has reported the development of premature atherosclerosis in patients who became diabetic by reason of pancreatic disease such as fibrosis, calculi, and so on. Although this is not thoroughly documented, there seem to be, in the human being, examples of premature vascular disease coming on as a result of induced diabetes presumably without relation to any hereditary factor.

Heat Therapy for Ischemia in the Lower Extremities

The Use of a New Thermostatically Controlled Therapeutic Heating Box

Kenneth R. Woolling, M.D., and Clifford Wilson,† Indianapolis*

It is the purpose of this paper to describe a method of controlled heating which the authors believe may be safely used to promote vasodilatation and aid in the healing of ulcers and infections and in the relief of rest pain in ischemic extremities.

It is generally agreed that the optimal environmental temperature for the ischemic limb lies between 90° F. (32.2° C.) and 95° F. (35° C.).[1-7] Temperatures higher than 100° F. (37.7° C.) may be harmful. Heating boxes or cradles are frequently placed over the lower extremities therapeutically to provide increased warmth. When the source of heat is one or two ordinary incandescent lamps, we have found that, although there is thermostatic control, the temperature in the lamps and in the region immediately around them intermittently reaches levels in excess of 120° F. (48.9° C.). If the lamps are shielded, the shields in turn become excessively hot. This would be of no importance if one could be sure that the patient would keep the legs in the center of the space provided by the box or cradle, where the temperature is at the desired level; however, not infrequently during sleep or inadvertently while awake, particularly if there is impaired sensation, the patient may bring the feet or legs in contact with the heating units or shields and a burn may result. On the other hand, if the lamps are too well shielded, insufficient heat reaches the therapeutic compartment. It seemed to us desirable to construct a box in which no "hot spots" develop, yet in which at the same time a therapeutic degree of heat can be maintained and more uniformly distributed. We have found the following arrangement to be satisfactory.

DESCRIPTION OF HEATING BOX

Using half-inch plywood, a box is constructed consisting of two sides, a top, and an end. The top surface of the opened box measures 68 cm. in length and 81 cm. in width, the sides 68 cm. in length and 40.5 cm. in height, and the end 81 cm. in width and 40.5 cm. in height. The entire assembly when not in use may be folded into a unit resembling a suitcase (figure 1).*

The heating unit, a thermostat,† and a thermometer‡ are mounted near the end of the box. The heating unit consists of twelve incandescent lamps§ mounted on a board bridging the lower border of the box end. The lamps are wired as four groups, with three lamps in each group, and the thermostat is connected with the circuit. Each of the three lamps comprising a group is connected in series with the other two lamps of the group, and each of the four groups is connected in parallel with the other three groups (figure 2). The pattern of mounting the individual lamps in the same group is staggered in a special manner, so that no two lamps belonging to the same group are side by side. A hinged panel is mounted on either side of the end of the box (figure 1). The thermostat is mounted on the wall between the two hinged panels; also in this wall is a lucite window in which the thermometer is mounted. The thermometer can be read from the outside of the box. On the outer surface of the end of the box is a recessed knurled knob by which the thermostat may be regulated. The heating unit is separated from the therapeutic compartment of the box by a sheet of galvanized wire screening

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*The outer framework of the box is similar to but not identical with the structure of leg cradles originally developed by the Vascular Section of the Mayo Clinic.

†Bimetallic thermoregulator, Cenco-DeKhotinsky, Central Scientific Co., Chicago, U.S.A.

‡No. 9610-A, Arthur H. Thomas Co., Philadelphia, U.S.A.

§40-watt, 120-volt showcase type bulb with inside frosting; outside dimensions 11 by 1 in.

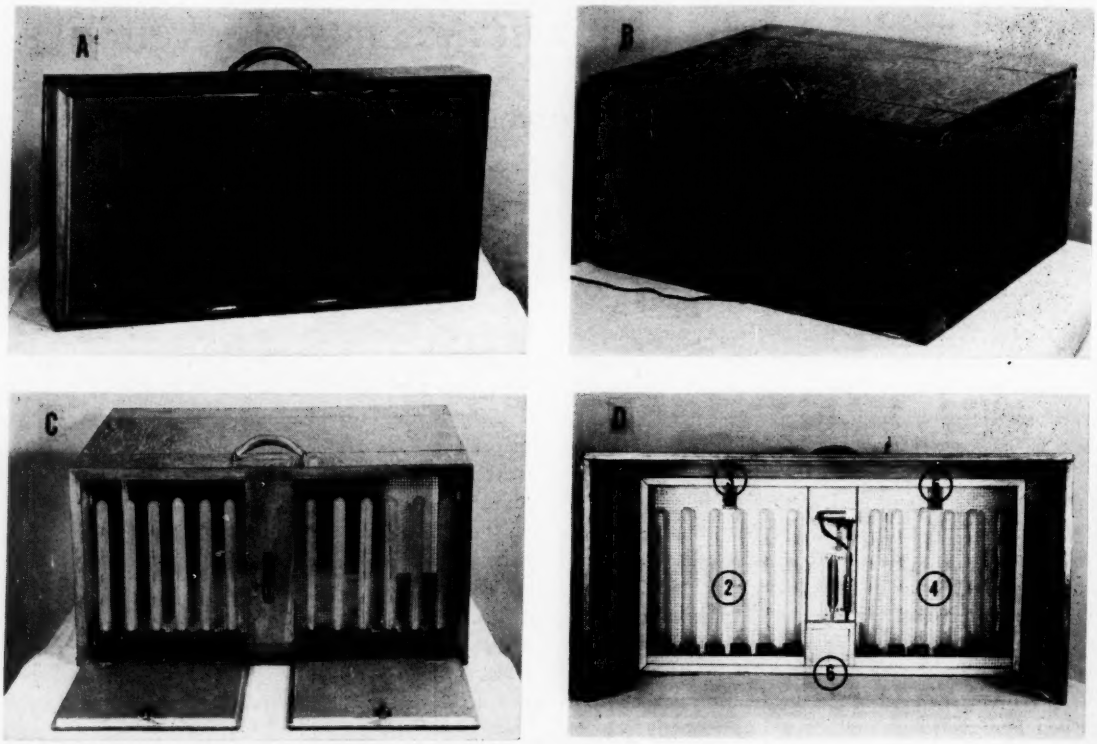

FIG. 1 New thermostatically controlled heating box. (A) Box closed for easy carrying when not in use. (B) Box unfolded ready for use. (C) Hinged panels on end of box opened to show accessibility to lamps for replacement. (D) Interior of box, showing heating unit, thermostat, and mounted thermometer. The arabic numbers indicate location of thermocouples during recording of temperature studies shown in figure 4.

(quarter-inch mesh) extending from side to side and from top to bottom. The distance between the end of the box and the galvanized screen is 9 cm.; each lamp (diameter 2.5 cm.) is mounted exactly midway between the screen and the end of the box. The entire inner surface of the box is lined with aluminum foil reflective insulation. The wire cord for connection with an electrical outlet is attached at the lower central portion of the heating unit. The hinged panels can be opened to permit access for removing or replacing a lamp.

During use, the opened box is placed over the foot of the bed and anchored by spreading a full-length bed sheet crosswise over the top of the box, tucking the ends of the sheet under the mattress on either side, and, finally, covering with the usual bed covers (sheet, blankets, and bedspread), which are placed over the anchor sheet and draped from the top of the box down over the patient (figure 3). When in use, the only portion of the box not covered is the end, on which may be seen the thermometer observation window and the thermostat regulator knob.

On connecting the cord with a wall outlet, the lamps illuminate and the temperature inside the box gradually rises (figure 4). The thermostat is then adjusted so that the lights go off when the thermometer mounted in the box registers between 89° and 90° F. After the initial adjustment, no further change in the setting of the thermostat is necessary. The greatest fluctuation and the highest temperature are noted initially, following a cold start, but after the box becomes warm the range of fluctuation of temperature is less. During this study the temperatures within the box were determined by use of a Brown Potentiometer.* This instrument is equipped with six thermocouples with an automatic device for consecutive recording of the temperature of the individual thermocouples. The six thermocouples were utilized simultaneously and continuously for study for

*The Brown Instrument Regulator Co., a division of Minneapolis-Honeywell, Philadelphia.

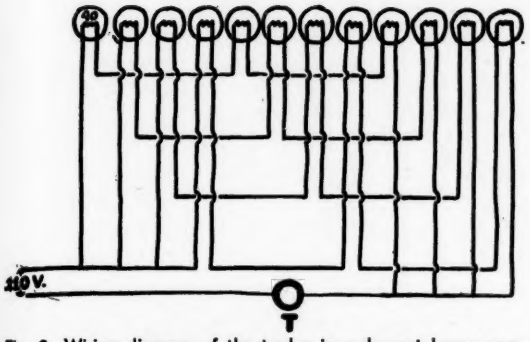

Fig. 2. Wiring diagram of the twelve incandescent lamps comprising the heating unit.
T equals thermostat.

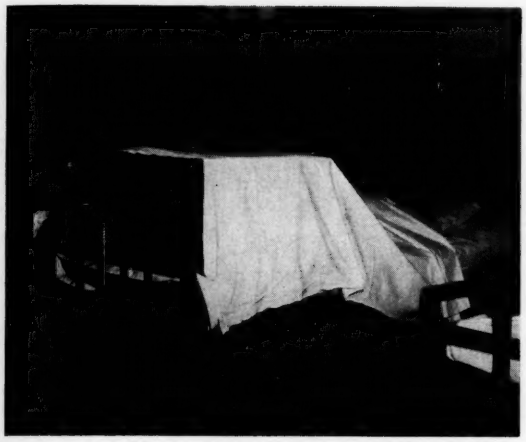

Fig. 3. Heating box in use on hospital ward.

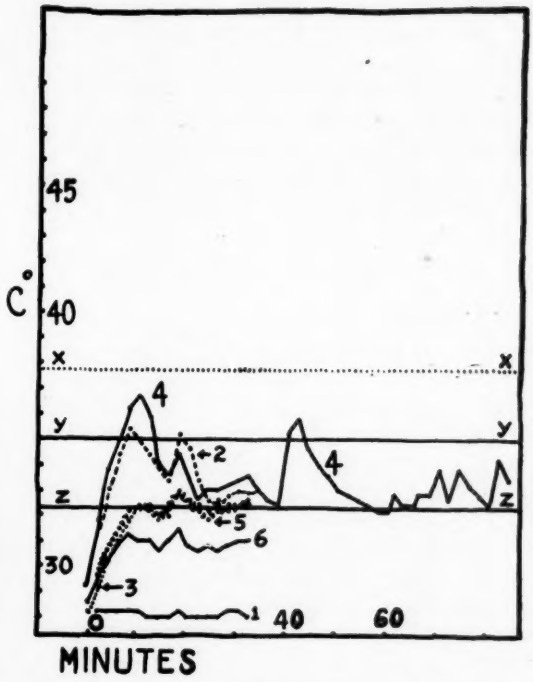

Fig. 4. Record of temperature at different points in heating box during use.
After initial warming, the temperature indicated by the thermometer visible through the window in the end of the box was 90°F. plus or minus 1°F. during the period shown in the graph above.
#1—Room temperature.
#2 to 6—Temperature at points within the box indicated in figure 1-d.
Dotted horizontal line (x) represents 100°F. (37.7°C.); upper solid horizontal line (y), 95°F. (35°C.); lower solid horizontal line(z), 90°F. (32.2°C.). Zone yz represents ideal temperature range; x is upper limit of safe temperature range.

periods up to eight hours; five were placed within the box, and one was placed outside to register the temperature of the room. The thermocouples inside were placed at representative points, some as near as possible to the lamps and others near the center of the heating space (figure 1-d). When one or more groups of lamps were extinguished during testing, the location of the thermocouples was changed so as to detect the highest temperatures near the remaining illuminated lamps as well as in the center of the heating space.

The arrangement permitted maintenance of an optimal temperature at all points inside the box within reach of the patient's extremities. When the thermostat was adjusted so that the temperature indicated by the thermometer mounted in the observation window in the end of the box was 90° F. (32.2° C.), the temperature at points tested inside the therapeutic compartment never exceeded 97.9° F. (36.6° C.) or fell below 87.1° F. (30.6° C.) (figure 4); the temperature at points nearest the heating unit (figure 1-d, #2, 3, 4, and 5; figure 4) ranged for the most part between 90° F. (32.2° C.) and 95° F. (35° C.). Thus, when the temperature was 90° F. (32.2° C.), as read from the mounted thermometer viewed from the outside, the temperature inside the therapeutic compartment was in a safe and, for the most part, an ideal range.

Individual temperature studies with one, two, or three of the groups of lamps extinguished disclosed that, although the duration of the heating curve was longer with fewer lamps simultaneously illuminated, the highest temperature achieved in any such arrangement was 97.7° F. (36.6° C.) and the lowest was 85.3° F. (29.6° C.). This fact adds a safety factor which would operate in the event that the burning out of one or more of the

lamps should occur and not be discovered for a matter of hours. Burned-out lamps should be replaced, however, since a therapeutic degree of warmth is not so well achieved with fewer than the twelve lamps illuminated simultaneously. The assembly has been in continuous operation for as long as thirty-five days, and the temperature indicated by the built-in thermometer varied no greater than 1° F. (between 89.5° and 90.5° F.). No lamp burned out during this time.

COMMENT

We believe that this method of controlled heating is applicable in the treatment of the majority of patients who have chronic occlusive arterial disease with the common complications of ulceration, rest pain, or infection in the lower extremities. The box described is an improvement over former models in that it offers additional safeguards against burning. The box also functions as a cradle preventing pressure and friction from the bedclothes on ischemic lesions. The box is large enough to allow considerable freedom of movement of the limbs within it. It has proved valuable in maintaining optimal warmth of local moist applications and has permitted ready access to the patient's limbs for inspection, local treatment, and change of dressings.

It is to be emphasized that heat therapy with this box is only one of a number of methods of treatment applicable to hospital cases of chronic occlusive arterial disease. In almost all instances, it is used in combination with other conventional therapeutic measures, which have been described elsewhere.[8]

Occasionally, a patient is encountered in whom increased discomfort in the limb is experienced when the box thermometer registers 90° F. (32.2° C.). In such cases, we have found that the box may be well tolerated if the thermostat is readjusted so that the temperature indicated in the observation window is approximately 85° F. (29.4° C.). The box should not be used in cases of acute or very recent peripheral arterial occlusion, or in cases with impending gangrene of a major portion of the foot or leg, since the profound ischemia of the limb and very meager available collateral blood flow may render the extremity extremely vulnerable to harm from any exogenous heat.

SUMMARY

This paper describes a modified thermostatically controlled heating box in which a safe as well as effective temperature is provided at all points within the therapeutic compartment. During use, actual recorded temperatures remained between 87.1° F. (30.6° C.) and 97.9° F. (36.6° C.). The box is to be used as an ancillary form of treatment for hospital patients who have local complications of chronic occlusive arterial disease of the lower extremities. It is our belief that this box is an improvement over heating cradles in current usage, since it offers additional safeguards against burning.

ACKNOWLEDGMENTS

We wish to express our appreciation of the assistance and extremely helpful suggestions and criticism given by Dr. Kenneth G. Kohlstaedt, Director of the Lilly Laboratories for Clinical Research, and Mr. John L. Woolling, M.Sc., Ch.E.

SUMMARIO IN INTERLINGUÁ

Thermotherapia in Ischemia del Extremitates Inferior: Le Uso de un Nove Cassa Thermotherapeutic a Regulation Thermostatic

Le presente articulo describe un modificate cassa thermotherapeutic a regulation thermostatic in que un efficace e nonriscose temperatura es providite a omne punctos intra le compartimento therapeutic. In uso practic le temperatura observate per registration objective remaneva intra 30,6 e 36,6 C. Le cassa es destinate al uso ancillari in le tractamento de hospitalisate patientes con complicationes local de chronic arteriopathia occlusive del extremitates inferior. Nos crede que iste cassa es melior que le cunas thermotherapeutic nunc in uso proque illo offere garantias additional contra possibile ardituras.

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Hypothyroidism and Diabetes Mellitus

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The role of the thyroid hormone in the regulation of carbohydrate metabolism is evident from the alterations of the latter which follow changes in thyroid function. Increased rate of absorption of ingested sugars,[1] slight hyperglycemia,[2] and glycosuria[3] often occur in thyrotoxicosis,[2] whereas a decreased rate of absorption of sugar occurs in hypothyroidism.[1] These alterations of carbohydrate metabolism associated with changes in thyroid function are rarely of any clinical significance in the nondiabetic individual. However, changes in thyroid function produce marked alteration in the impaired carbohydrate metabolism of patients with diabetes mellitus; the severity of diabetes is increased in the presence of thyrotoxicosis,[2] and often ameliorated by hypothyroidism.[4] Likewise, diabetes is more frequent in patients with thyrotoxicosis than in the general population,[5] whereas hypothyroidism and diabetes mellitus rarely develop in the same patient.

Thirty-three cases of hypothyroidism and diabetes have been reported. The diabetes preceded the hypothyroidism in eighteen of the cases,[2, 5-14] and in twelve it developed while the hypothyroidism was being treated.[2, 6, 7, 15-21] In only three patients were the two diseases diagnosed at the same time.[2, 22, 23] Eight other cases reported as instances of hypothyroidism coexisting with diabetes mellitus are unacceptable because of inadequate evidence for diagnosis of hypothyroidism; in two cases the diagnosis of diabetes was also in question.[24-29] Diabetes and hypothyroidism have occurred in patients with various types of multiple glandular disorders: pituitary myxedema,[30] pituitary tumor,[31] and pseudopituitarism.[32-34] The case report by Schuman[30] is the only example of diabetes mellitus and pituitary myxedema not associated with evidence of other pituitary failure or tumor. The possibility that some of the cases referred to above were instances of pituitary myxedema cannot be evaluated since the response to thyrotropic hormone[35] which would separate primary hypothyroidism from pituitary hypothyroidism was not determined.

In view of the rarity of reports of cases of diabetes mellitus associated with hypothyroidism it was considered of interest to present the case studies of two patients who had both diseases. One was a case of spontaneous myxedema with impaired carbohydrate tolerance in which clinical signs of diabetes mellitus developed after nine years of treatment with thyroid substance. The second case was that of an untreated adult cretin.

Case 1. A. P., a forty-nine-year-old woman clerk, was admitted to the Medical Service of Jefferson Medical College Hospital in 1944. She complained of asthenia, increasing weight, hypersomnolence, and sensitivity to cold for the past six years. The menstrual periods ceased in 1936. She also was diagnosed as having a paranoid-schizophrenia.

At physical examination the pulse varied between 50 and 60 and the blood pressure was 100/62. The hair was dry, coarse, and somewhat sparse. The complexion was pale and pasty and the skin was dry and coarse. There was nonpitting edema of the extremities. The speech was slow and slurred. The findings were typical of severe hypothyroidism and the laboratory studies confirmed the clinical impression.

The hemoglobin was 72 per cent, the red blood cell count 3,200,000, and the white cell count 7,200. The serum cholesterol was 333 mg. per 100 ml. and the basal metabolic rate was —30. The fasting blood sugar was 66 mg. per 100 ml. Impaired glucose tolerance was evidenced by the oral test: the fasting blood sugar was 60 mg. per 100 ml.; the blood sugar was 96 mg. per 100 ml. after ingestion of glucose, 160 mg. at two hours, 148 mg. at three hours, and 178 mg. at four hours. The 17-ketosteroid excretion was 1.8 mg. per twenty-four hours. The electrocardiogram showed low voltage in all complexes, with flattening or inversion of the T waves in all leads.

Treatment with thyroid substance, 90 mg. daily, was started and the symptoms of hypersomnolence and asthenia, as well as the physical findings of hypothyroidism, disappeared. The electrocardiogram reverted to normal. However, there was no change in the mental aberration. In 1953, the patient developed progressive weight loss, polyuria, polydypsia, and pruritus

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vulvae; glycosuria and hyperglycemia were present. Daily treatment with 40 units of NPH insulin was followed by relief of symptoms.

Subsequently the patient discontinued thyroid medication and was readmitted to the medical service six months later. At that time she again had signs and symptoms of severe hypothyroidism, and laboratory studies confirmed the clinical diagnosis. The hemoglobin was 78 per cent, the red cell count 4,000,000, and the white cell count 7,400. The cholesterol was 385 mg. per 100 ml. The protein-bound iodine was 2 microgm. per 100 ml., and the uptake of radioactive iodine after twenty-four hours was 1 per cent. The electrocardiogram again showed low voltage of the QRS complexes and flattened or inverted T waves in all leads. The patient had no glycosuria, and the fasting blood sugar varied between 66 and 112 mg. per 100 ml. The glucose tolerance was impaired; the blood sugar was 112 mg. fasting, 185 mg. one hour after ingestion of glucose, 180 mg. at two hours, and 200 mg. at three hours. The electroencephalogram showed low voltage and a slow rhythm. Treatment of hypothyroidism was followed by a recurrence of hyperglycemia, glycosuria, and need for insulin.

Case 2. A. I., a thirty-eight-year-old woman of Italian descent, was first admitted to the Medical Service of Jefferson Medical College Hospital in June 1952 because of decreasing visual acuity. Her twin sister and her older brother, the only other siblings, developed normally. There was no family history of thyroid disorders. Her rate of growth had been abnormally slow. The first teeth appeared at the age of three years. The patient neither talked nor walked until the age of five years. She had never menstruated. Her family did not seek medical advice until she was thirty-eight years old.

At physical examination there were immature cataracts in both eyes. The head hair was coarse and somewhat sparse. Axillary and pubic hair were sparse. The complexion was pasty; the skin was dry. The tongue was thicker than normal. The patient was apathetic and slept most of the time.

The hemoglobin was 78 per cent, the red cell count 4,000,000, and the white cell count 9,000.

Urinalyses showed 1 to 2 per cent glycosuria and a trace of protein. The reducing substance in the urine was fermented by yeast, and did not react with Seliwanoff's reagent. The plasma proteins were 6.42 gm. per 100 ml.; the albumin-globulin ratio was 1.9. The serum bilirubin was 0.4 mg. per 100 ml., cephalin flocculation plus 1, and thymol turbidity 2.0 units. A bromsulfalein test showed no retention. The oral glucose tolerance test showed the following blood sugar values: 400 mg. fasting; 400 mg. one hour after ingestion of glucose, 526 mg. at two hours, 530 mg. at three hours, and 328 mg. at four hours. The result of the insulin tolerance test (0.1 unit of crystalline insulin per kilogram of body weight by the intravenous route) was as follows: the blood sugar was 504 mg. fasting, 390 mg. fifteen minutes after injection, 400 mg. at thirty minutes, 400 mg. at forty-five minutes, 360 mg. at one hour, 400 mg. at one and a half hours, and 360 mg. at two hours. The urinary excretion of 17-ketosteroids was 4.0 mg. per twenty-four hours. Urinary gonadotropins were not demonstrable at the level of 6 mouse uterine weight units per twenty-four hours. A vaginal smear showed marked estrogen deficiency. The protein-bound iodine was 2.0 microgm. per 100 ml. The uptake of a tracer dose of I-131 after twenty-four hours was 6 per cent. A roentgenogram of the chest showed the transverse diameter of the heart at the top limit of normal based on the cardiothoracic ratio. The roentgenograms of the long bones showed an increase in thickness and marked decrease in length, and many of the epiphyses were incompletely fused. The pattern of fusion of the epiphyses was irregular inasmuch as the cartilaginous junction between the ischium and pubis, which normally closes between the seventh and eighth year, was still partially open, while other epiphyses which do not fuse until the eighteenth or twentieth year were closed. The electrocardiogram showed depression of the T wave in all leads.

During the period of hospitalization the patient developed a urinary tract infection and had fever up to 102°F. for ten days. Although no insulin was administered and she consumed a 1,400 calorie diet, ketosis did not develop. When she was afebrile the same diet was continued and 30 units of protamine zinc insulin was administered daily before breakfast. The glycosuria disappeared and the fasting blood sugar was reduced to 125 mg. per 100 ml. She did not receive thyroid substance at this time.

In June 1953 the patient was readmitted because of ankle edema and increasing dyspnea. She had received 30 units of protamine-zinc insulin daily but had taken no thyroid substance. She had gained 31 pounds. The findings were unchanged except for the presence of pitting edema of the ankles, cyanotic hue of the lips, and signs of pulmonary congestion. The hemoglobin was 76 per cent, the red cell count 3,800,000, and the white cell count 8,100. The bone marrow nucleated count was 85,000. Frequent urinalyses were negative for glucose. The blood urea nitrogen was 10 mg. per 100 ml., and plasma proteins were 6.82 gm. per 100 ml. The serum calcium was 9.0 mg. per 100 ml., the serum phosphorus was 3.7 mg. per 100 ml., and the alkaline phosphatase was 5.3 Bodansky units per 100 ml. The fasting blood sugar was 143 mg. per 100 ml.

During this period of hospitalization, treatment with protamine zinc insulin was continued and the fasting blood sugars varied between 143 and 200 mg. A roentgenogram of the chest at the time of admission revealed an increase in the transverse diameter of the heart with evidence of pulmonary congestion. The electrocardiogram showed left axis deviation with inversion of the T waves. The intelligence quotient determined by the Stanford-Binet form L test was 36. The electroencephalogram showed an abnormally slow rhythm in all leads. The 17-ketosteroid excretion was 1.2 mg. per twenty-four hours. Urinary gonadotropins were not demonstrable at a level of 6 mouse uterine weight units. Urinary excretion of 11-oxysteroids after enzyme hydrolysis as determined by a modification of the Porter-Silver technique was 900 microgm., an abnormally low value. The uptake of radioactive iodine by the thyroid gland twenty-four hours after a tracer dose was again 6 per cent; the protein-bound iodine was 0.6 microgm. per 100 ml. Following administration of 10 mg. of thyrotropic hormone, three times daily for three days, the radioactive iodine uptake was 5 per cent and the protein-bound iodine remained at 0.6 microgm.

The patient was treated with 30 mg. of thyroid U.S.P. daily. The only noticeable change was disappearance of the edema and pulmonary congestion.

DISCUSSION

Case 1 is another instance of the occurrence of diabetes mellitus in a patient with treated myxedema. The patient had the classical clinical manifestations of severe hypothyroidism-asthenia, hypersomnolence, sensitivity to cold, dry, coarse hair, and a dry thick skin with nonpitting edema of the extremities. The laboratory reports of low basal metabolic rate, high cholesterol, and electrocardiographic changes confirmed the diagnosis. In addition to the hypothyroidism, the patient also had a decreased tolerance for carbohydrate inasmuch as the blood sugar was 178 mg. per 100 ml. four hours after the ingestion of 100 gm. of glucose. Treatment with desiccated thyroid resulted in the disappearance of the clinical manifestations of hypothyroidism, the basal metabolic rate increased to normal levels, and the electrocardiogram returned to normal. Nine years after starting treatment with desiccated thyroid, the patient developed weight loss, polyuria, polydypsia, pruritus vulvae, hyperglycemia and glycosuria. These symptoms were ameliorated by insulin. When the thyroid medication was stopped the need for insulin disappeared and the manifestations of severe hypothyroidism recurred. The impairment of carbohydrate metabolism was not much greater at this time than it had been at the time the diagnosis of myxedema was first made.

This case may be added to the twelve reported cases of diabetes appearing in hypothyroid individuals treated with thyroid hormone.[2, 6, 7, 15-21] These observations should probably be interpreted as indicative of a precipitation of a latent into frank diabetes by the administered thyroid hormone rather than of causation of diabetes by the latter. This interpretation is supported by the finding in our Case 1 of an impaired carbohydrate tolerance before any thyroid medication was administered. Other clinical and experimental observations lend further support to this thesis. Thyrotoxicosis causes the earlier appearance of diabetes mellitus in patients with potential diabetes,[5] but not in those with normal pancreatic function.[36] Likewise, total thyroidectomy will decrease the severity of the diabetes,[5] but treatment of the resultant hypothyroidism, with the elevation of the basal metabolic rate to normal, is followed by a return of the more severe manifestations of the diabetes.[5, 37] Similar observations have been made in experimental animals. Excessive thyroid hormone will produce diabetes mellitus in animals with impaired pancreatic function, but not in normal animals.[36] Likewise, early thyroidectomy prevents the onset of diabetes in partially pancreatectomized rats.[34] Treatment with thyroid extract of the thyroidectomized, partially depancreatectomized rat, started at the time of the operations, permitted the development of the diabetes.[36] The studies in experimental animals as well as the observations in human beings suggest that alterations of thyroid function result in significant alterations in carbohydrate metabolism only when the pancreatic function is impaired.

In contradistinction, the occurrence of hypothyroidism in 18 cases with pre-existing diabetes[2, 5-14] is probably coincidental in view of the fact that there is no evidence of impaired thyroid function resulting from diabetes mellitus. Whereas there appears to be no causal relationship between the two diseases, the hypothyroidism decreases the severity of the diabetes, as discussed above.

Case 2, together with three cases found in the literature,[2, 22, 23] represents the rare simultaneous occurrence of severe untreated hypothyroidism and frank diabetes. Our case appears to be the only one of the four in which diabetes was associated with cretinism. The case reported by Greenwald and Collens[1] was that of a cretin treated for seven and one-half years before the development of diabetes. Wilder's[5] patient developed diabetes at the age of fifteen months and hypothyroidism at the age of twenty-one months. One of Joslin's[3] cases had both hypothyroidism and diabetes at the age of nine years, but was not a cretin.

The diagnosis of cretinism in our case was based on the history and physical findings: decreased growth rate, dwarfed stature, and mental retardation. The impairment of thyroid function was confirmed by the low protein-bound iodine and low thyroid uptake of radioactive iodine. Failure of elevation of the values of the protein-bound iodine and radioactive uptake following administration of thyrotropic hormone strongly suggests that the hypothyroidism was due to primary thyroidal failure rather than secondary to pituitary failure.

The patient later developed congestive heart failure as a result of "myxedema heart disease." Signs of edema as well as the pulmonary congestion were relieved by desiccated thyroid.

The diabetes mellitus in this patient showed some unusual features. Whereas the diabetes was rather severe as judged by the degree of hyperglycemia and glycosuria, she was resistant to the development of ketosis; no ketosis occurred when the patient developed a urinary tract infection at a time when she was not receiving insulin. The resistance to the development of ketosis in this untreated cretin may be related to the decrease of ketone body production in hypothyroidism. Furthermore, the level of hyperglycemia was not increased by the

urinary tract infection. Also, the amount of insulin required to induce normoglycemia was not increased when the patient ultimately was treated with thyroid hormone. In this respect the metabolic response in this individual differs from that usually observed in diabetics in whom the insulin requirement is markedly dependent on the levels of thyroid hormone. The reasons for this unusual irresponsiveness of diabetic metabolism both to infection, and to a rise of thyroid hormone, is unknown.

Both patients excreted small amounts of 17-ketosteroids in the urine; the cretin excreted very small amounts of 11-oxysteroids. The decreased amounts of 17-ketosteroids and 11-oxysteroids excreted by patients with hypothyroidism probably reflects the decreased adrenocortical function which may develop in patients with decreased thyroid function.[38] However, neither of these patients had any clinical manifestations of adrenal insufficiency.

SUMMARY

The case reports of two patients who had diabetes and hypothyroidism are presented. In one patient the diabetes appeared nine years after the institution of treatment of the hypothyroidism. The clinical manifestations of the diabetes and the need for insulin disappeared when the hypothyroidism was permitted to return. The second case was that of an untreated adult cretin who had diabetes when first seen.

SUMMARIO IN INTERLINGUA

Hypothyroidismo e Diabete Mellite

Es presentate le casos de duo patientes con diabete e hypothyroidismo. In un del patientes le diabete appareva 9 annos post le initiation del tractamento pro hypothyroidismo. Le manifestationes clinic del diabete e le requirimento de insulina dispareva quandocunque le retorno del hypothyroidismo esseva permittite. Le secunde patiente esseva un non previemente tractate cretin de etate adulte qui habeva diabete al tempore del prime examine.

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Altered Protein Metabolism in Disease and Injury

In disease and injury, protein metabolism may be adversely affected in several ways. First, the reduced appetite associated with disease almost always reduces both caloric and protein intake. This would tend to induce the body to burn up its carbohydrate, fat, and protein stores, which, if of insufficient magnitude, would alone cause primary hypoproteinia. Early ambulation has contributed to the mitigation of this factor by restoring appetite earlier.

Second, in gastrointestinal conditions, digestion and absorption may be affected adversely, and discharge from fistulas, or diarrhea, may side-track the alimentary stream or prevent absorption.

Third, large losses of nitrogen from the body could occur through the loss of biological fluids, drainage, blood loss and body exudates. We have shown, for instance, that in burns, over 19 gm. a day of nitrogen can be lost in the exudates from the burned area. The seepage of cerebrospinal fluid, or of the discharge from a profusely draining sinus, could likewise cause considerable protein loss.

Fourth, immobilization and bed rest cause nitrogen loss, which has been interpreted by Cuthbertson and by Deitrick *et al* as being due to the atrophy of disuse. This also is minimized by early ambulation.

Fifth, the "toxic destruction of protein," as expressed by the increased nitrogen excretion of the catabolic period, is more pronounced in the normoproteinic than in the hypoproteinic. Albright and Browne *et al* have related this to Selye's "alarm reaction." The azoturia may reach a level of over 20 gm. of nitrogen a day. This phenomenon has been linked to the heightened secretion of the glucocorticoid hormones from the adrenal cortex, presumably either cortisone or hydrocortisone, both protein catabolic agents. This effect has been studied by Browne, Howard, Grossman *et al* and recently by Moore. This reaction is thought to be irreversible, because such high daily intakes of nitrogen as 20 gm. (135 gm. protein) do not reverse the nitrogen balance. Food proteins given during this "catabolic period," or period of "obligatory protein rejection" (formerly thought to last weeks, but now a few days) are presumably burned and eliminated.

The teleological explanation for this was thought to be an effort of the organism to mobilize amino acids from its own tissues for the purpose of repair. According to the irreversibility theory, during this "natural" period of "obligatory protein rejection," the body not only must destroy some of its own tissues, but the mechanism mobilized for this purpose is so indiscriminate that this destruction cannot be prevented even if amino acids are made available from outside sources.

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Diabetic Acidosis: Prevention and Treatment

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Diabetic acidosis is one of the most dramatic of medical emergencies. The patient who develops this condition may within a few days pass through the successive stages of dehydration, ketosis, coma and death. This progression of events can be entirely prevented if the condition is recognized and treated in time.

The prevention of diabetic acidosis depends on thorough understanding of diabetes by both the patient and his physician. This complication may threaten any diabetic, under the stress of an acute infection, or other illness, trauma or surgical operation. Under these circumstances, insulin may be needed in large dosage, even in cases previously treated successfully with diet alone. If this need is not met, acidosis may result. Both the physician and the patient must be alert to the danger; if the proper steps are taken, acidosis will not occur. The patient should be encouraged to telephone his physician regarding even minor illnesses. He should be taught to test his urine every four to six hours during an illness; heavy glycosuria will warn him of impending trouble. Additional doses of quick-acting (regular or crystalline) insulin, the amount depending on the degree of glycosuria each time will usually prevent the occurrence of acidosis. A dosage schedule commonly recommended is: 20 units for a red test, 15 units for orange, 10 for brown, and 5 for green. A smaller amount should be employed for a child, or for the adult who is subject to hypoglycemic reactions.

Most patients admitted to the hospital in severe acidosis have failed to seek medical advice during the early stages of this disorder. Some of these have not previously known that they had diabetes. The incidence of such cases can be reduced only by education of the public regarding the symptoms of diabetes, and by the practice of periodic health examinations. Other patients are those with treated diabetes who have become increasingly careless in following their diabetic regime. Such patients neglect the diet, stop testing the urine and allow appointments with the physician to lapse. Often a trifling infection upsets their precarious balance, and when vomiting sets in, they may commit the final error of omitting the essential insulin injections. Since many of these patients, after recovery from acidosis, make certain that it never occurs again, it is probable that the initial episode was due in part to a failure to appreciate the danger. Thus education of the patient must play an important role in preventing this complication. The physician, by taking pains to give the patient and his family thorough instruction in diabetes, and by establishing and maintaining a cordial and sympathetic relationship, can greatly reduce the likelihood of this complication.

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DIAGNOSIS

Diabetic ketosis is easily recognized by finding acetone in the urine or by detecting the odor of acetone on the breath. Ketosis of slight degree is a common occurrence when diabetes is only mildly out of control, particularly in cases of unstable or "brittle" diabetes. Hence, the presence of acetone in the urine or on the breath need not of itself cause alarm, although it should definitely put the physician on guard. The *absence* of ketosis today is of course reassuring, but affords no guarantee that it will not be present in a serious degree tomorrow. It is important to realize that diabetic acidosis has an insidious nature, and that the patient does not appear ill until the process is well advanced. It is therefore the task of the physician to evaluate the diabetic state of his patient each time he is consulted and especially when the patient calls him for some other illness. A history of increased volume and frequency of urination, of thirst and weakness, along with the finding of much sugar and acetone in the urine indicates the presence of ketosis which could quickly become serious. If in addition the patient reports anorexia, vomiting and abdominal pain; and if the physician notes a parched tongue, air hunger and drowsiness, a dangerous state of acidosis must be present.

Further laboratory tests are often helpful in evaluating the patient's diabetic status, although in practice the immediate decision as to the plan of treatment will be governed by the patient's appearance. In general, the higher the blood sugar, the more alarming the situation.

A blood sugar of 250 mg. is usually reassuring, but it should be remembered that occasionally diabetic coma is encountered with the blood sugar no higher than this. A depressed plasma carbon dioxide combining power, on the other hand, is almost always significant, and a positive serum acetone test[1] is a sure indication of a serious degree of ketosis.

If the diabetic patient is unconscious, a special problem is presented. Is the coma due to hypoglycemia, or to acidosis, or to some condition unrelated to diabetes? A history of sudden onset (in less than two hours) combined with the presence of profuse sweating justifies immediate treatment for hypoglycemia. A history of illness for more than twenty-four hours culminating in coma, combined with the presence of air hunger and dehydration, makes the diagnosis of diabetic coma almost certain. In such a situation treatment with insulin should be started without waiting for confirmatory laboratory reports.

TREATMENT

The milder degrees of ketosis may be treated safely at home. The patient is instructed to take his usual dose of insulin, and in addition, to take small doses of quick-acting insulin before meals and at bed-time according to the degree of glycosuria. If he has an illness which makes it difficult for him to remain on his usual diet, he is instructed to take small amounts of liquids and soft solids every hour or two. The physician should of course maintain close contact to assure himself that these orders are being carried out and are resulting in satisfactory control. If the illness is such as to interfere with an adequate oral intake, or if the physician has any doubt about the ability of the patient or his family to follow the instructions, it is wise to hospitalize the patient so that fluids may be given intravenously and closer supervision may be maintained.

For patients with a severe degree of acidosis, immediate hospitalization is imperative. The situation then calls for prompt and vigorous treatment, and for the full-time attention of the physician until recovery is assured. Any delay in initiating treatment may prove fatal; hence the first dose of insulin, 50 to 100 units, should be given as soon as the diagnosis is reasonably certain. A solution of isotonic sodium chloride should also be given by venoclysis as soon as possible. Blood should be drawn at once for determination of the blood sugar and the serum CO_2 content. (Other blood tests, such as the blood *p*H, hematocrit, nonprotein nitrogen and serum chloride may be helpful; and if the laboratory has a flame photometer the serum sodium and potassium should be ascertained.) In addition to these measures, a Foley catheter should be placed in the bladder if the patient is unconscious or unable to void. An electrocardiogram taken at this point may be of help later in the recognition of a potassium deficiency. It is well to start a chronological chart on which is recorded at hourly intervals the vital signs, the fluid intake and output, the laboratory tests and treatment, so that the patient's progress may be more clearly followed.

Another procedure which is usually recommended at this time is gastric lavage, as the patient in acidosis often has a dilated, atonic stomach which is distended with secretions and a large amount of partly-digested blood. He is vomiting small amounts frequently, and is intensely nauseated and distressed; his pulse may be rapid and thready. Gastric aspiration and lavage will often produce marked relief of these symptoms and a gratifying improvement in the pulse and blood pressure. Furthermore, the patient will be able to accept oral feedings at an earlier hour if this procedure is performed.

When these preliminary measures have been completed the physician may now take time to review the situation and evaluate the patient's condition. A history and a physical examination are required for recognition of infection or other complicating conditions, and for evaluation of the severity of the diabetic state. It is important to realize that fatalities occasionally occur in cases that do not appear seriously ill on admission to the hospital.[2] It is for this reason that constant watchfulness is essential in the treatment of each case. It should be kept in mind that acidosis may simulate an acute abdominal emergency. However, unless there are cogent reasons for believing that there is a surgical emergency, operation should be postponed, because usually the symptoms and signs disappear as the diabetic state is corrected.

At this point the physician is faced with the question: How much insulin should I give, and how often should I give it? It is impossible to give a dogmatic answer to this question. A recent suggestion has been made[3] that the first dose be equal in units to one-half the blood sugar level; (for example if the blood sugar is 1,000 mg., 500 units would be given at once). A second dose would be given four hours later, its size depending on the response of the blood sugar in the interval. However, most physicians will prefer to give an hourly dose of insulin, gauging the size of the dose by the change in blood sugar level, the degree of glycosuria and ketonuria, and the patient's general condition. For patients who are only moderately ill, 50 units every hour or two should be sufficient; for those who appear

acutely ill, and especially for cases in which the blood sugar is over 700 mg. per 100 ml., a dose of 100 to 200 units every hour is advisable. It may be advisable to give half of each dose intravenously, particularly when a state of shock is present. The dosage recommended for children is not greatly different from that for adults; but infants may be expected to respond to considerably smaller doses, such as 10 to 20 units each hour. Using the above dosage schedule, the blood sugar level will usually begin to fall in two or three hours, and will thereafter fall quite steadily. Occasionally a case is encountered in which the expected fall in blood sugar fails to take place. In this event the dosage schedule should be revised upwards, perhaps doubled, until a definite lowering of the blood sugar has been attained. As the blood sugar reaches a range that is no longer alarming, let us say 250 to 300, the size of the doses should be markedly reduced, and the interval between injections lengthened.

A recent interesting study[4] has cast some doubt on the value of huge doses of insulin, and suggests that there is no appreciable reduction in mortality or increased speed of recovery when large doses are administered instead of moderate ones. However, until this work is fully confirmed, I shall continue to advocate large doses for the patient with a very high blood sugar or whose blood sugar and general state have not improved within a reasonable time.

It is recommended that the blood sugar be checked every two or three hours in the first twelve to twenty-four hours. But sometimes the physician must depend upon the urine test, which is a much less reliable guide. The serum acetone test, as suggested by Duncan[1] may be valuable; a decrease in the degree of ketonemia foreshadows the disappearance of the insulin resistance which is usually present at the beginning of treatment. When the serum acetone test becomes negative, insulin should be administered with caution to avoid serious hypoglycemia.

There is still considerable disagreement about the ideal fluid to be employed intravenously in the early hours of treatment. It is my impression that most of the experts in this country administer isotonic sodium chloride solution. A few add sodium lactate or bicarbonate to this solution, and a few prefer more dilute solutions. Many continue to give glucose, although the arguments against its use are to me quite convincing. Briefly, these arguments are: (1) The blood already contains an excess of sugar, and additional glucose raises the level and increases the dehydration of the cell. (2) Intravenous glucose, by raising the blood sugar, diminishes the value of the blood sugar test in following the progress of treatment. (3) Intravenous glucose with insulin hastens the withdrawal of potassium from the blood and increases the risk of fatal hypokalemia. (4) Careful studies[5] have indicated that patients given glucose in the early hours of treatment have a higher mortality and a slower recovery rate.

Although the use of glucose in the early hours of treatment appears to be contraindicated, the objections to its use disappear as the blood sugar approaches normal; indeed, it then becomes a highly desirable part of treatment, as it provides calories and protects the patient from hypoglycemia.

The total quantity of fluid administered by venoclysis will vary, depending on the size of the patient and the degree of dehydration. Large amounts of saline can produce edema, particularly in the elderly and in those with cardiac or renal disease. While most authorities advise rapid administration of the first liter or two of saline solution to combat shock, I believe that it is wiser to administer it at a rate which can be maintained for many hours without overloading. If shock is present on admission, or if the blood pressure drops toward shock levels during treatment, whole blood or plasma may be given to support the circulation. Other supportive measures such as epinephrine, caffeine and digitalis are occasionally indicated. Perhaps the most satisfactory fluid replacement therapy is that which can be given orally rather than intravenously. Most acidotic patients are unable to retain feedings at first, so that oral feeding must be delayed for a few hours, and then cautiously attempted as nausea subsides. Small amounts of broth, milk, fruit juices and oatmeal gruel may be given at frequent intervals, providing easily-digested food containing some calories and a considerable amount of potassium.

Replacement of potassium, to avoid the dangers of potassium deficiency during recovery, has become an established part of the therapy of diabetic acidosis. It should be remembered that most untreated acidotic patients have a normal or slightly elevated serum potassium because of the large amount of potassium escaping from the cells.[6] During the course of treatment, the potassium level quite regularly falls as potassium migrates back into the cells. If the serum potassium falls below the level of 2.5 mEq./L. it is a sign of danger. Clinically, potassium deficiency should be suspected if the patient develops muscular weakness, or feeble or gasping respirations; or cardiac disturbances[7] such as the appearance of murmurs, a gallop rhythm, tachycardia and a fall in blood pressure, particularly the dia-

stolic blood pressure. The electrocardiogram may give valuable evidence of potassium depletion,[8] showing progressive flattening of the T waves and lengthening of the Q-T interval.

This complication will rarely occur in the patient who is able to retain potassium-rich oral feedings starting within a few hours of admission. But in cases in which there is repeated vomiting or prolonged coma the danger of death in hypokalemia is very real. Potassium salts should therefore be added to the intravenous infusion as soon as it is established that the patient has an adequate urine output—not sooner, because of the risk of producing potassium intoxication in the oliguric patient. Sterile ampules of potassium chloride are available commercially, and may safely be given in a dose of 1 or 2 gm. (13.8 to 27.6 mEq.) in each liter of the clysis fluid. Even larger amounts, up to 10 gm. per liter (138 mEq.) may be administered when the chemical and clinical evidence clearly indicates the need.[6]

It has also been recommended that potassium salts be given by mouth as soon as the patient is able to retain oral medication. In one series[3] the *average* dose of orally administered potassium dibasic phosphate was 18.6 gm. (214 mEq. of potassium) and others have recommended potassium chloride 1 to 2 gm. (13.8 to 27.6 mEq.) by mouth every one to two hours. Various studies have shown that a large percentage of the administered potassium is retained, and that with adequate potassium therapy, the serum potassium is prevented from falling to critically low levels.

SUMMARY

Methods of prevention of diabetic acidosis are discussed, stressing thorough education of the patient, the maintenance of a good doctor-patient relationship, and the recognition of the earlier stages of ketosis. The treatment of severe acidosis is discussed with emphasis on prompt initiation of treatment, the need for constant attendance, and the importance of simple laboratory procedures such as blood sugar determinations in following the patient's course.

SUMMARIO IN INTERLINGUA

Acidosis Diabetic: Prevention e Tractamento

Es discutite methodos del prevention de acidosis diabetic. Le factores sublineate como specialmente importante include le detaliate education del patiente, le mantenentia de bon relationes personal de medico e patiente, e le recognition del precoce phases de cetosis. Le tractamento de sever acidosis es discutite. Le punctos hic sublineate include le importantia de prompte initiation del tractamento, le necessitate de constante surveliantia, e le valor de simple technicas laboratorial in sequer le curso clinic del patiente. Iste technicas include per exemplo le determination de sucro sanguinee.

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Recent Statistics on Diabetes

CURRENT MORTALITY DATA

The death rate from diabetes for the United States as a whole in the first half of 1955 showed little change from the corresponding period of 1954 (table 1). Provisional data based on a 10 per cent sample of death certificates collected by the National Office of Vital Statistics indicate a death rate of 15.9 per 100,000 compared with 15.8 in 1954. The urban wage-earning population, represented by the Industrial policyholders of the Metropolitan Life Insurance Company, had a death rate of 15.6 in the first half of 1955 compared with 15.4 in 1954.

The small rise in diabetes mortality in the first half of the year is remarkable in view of numerous outbreaks of respiratory diseases in February which resulted in a significant rise in the death rate of that month, particularly among persons with chronic disease. The death rate from all causes dropped subsequently, and by the end of June was down to the all-time low for the first six months, recorded in 1954.

In New York State, New York City, Maryland and Baltimore, the death rates from diabetes in the first half of the year were appreciably higher than those of 1954. The rates for Philadelphia and Boston in 1955 are not comparable with those available for 1954 because of a change in the basis of reporting of deaths for Philadelphia and a change in the classification procedure of diabetes deaths by the Boston Health Department.

The death rate from diabetes in the two largest Canadian cities, Toronto and Montreal, showed divergent trends between the two years. Both in London (Administrative County) in the first half of this year, and in England in the first quarter of this year, the rates were appreciably higher than in the previous year.

Regional data for the United States for the first half of 1955, based upon the 10 per cent sample of death certificates, showed a small increase in the death rate from the previous year in the Northeastern part of the country and an appreciable increase in the Southwest and Far West (table 2). Elsewhere there was a decline in the death rates. In part, these regional

Submitted by the Committee on Statistics, Herbert H. Marks, Chairman. The Committee welcomes suggestions or actual material suitable for this section in future issues, from Association members and other readers of the JOURNAL.

TABLE 1

Recent data on diabetes mortality
Deaths and death rates – January-June 1955 and 1954

Area	Death Rates per 100,000		Number of deaths	
	1955	1954	1955	1954
United States (10 per cent sample)	15.9	15.8	1,294	1,254
Metropolitan Life Ins. Co. Industrial Policyholders	15.6	15.4	1,399	1,391
New York State*	20.9	20.3	1,375	1,324
New York City	20.9	19.4	846	795
Maryland	17.1	16.2	220	205
Baltimore, Resident	20.3	17.6	98	85
Boston	10.3	27.0	41	108
Philadelphia	20.6	29.0	222†	312
Toronto	15.3	16.2	52	55
Montreal, Resident	19.3	19.2	104	102
London (Administrative County)	9.3	6.8	154	113
	Jan.-Mar.		Jan.-Mar.	
	1955	1954	1955	1954
England and Wales				
Total	9.2	8.4	1,009	918
Males	6.4	6.2	335	325
Females	11.9	10.5	674	593

*January-May
†Resident deaths

Note: Rates for the states and cities are based upon local estimates of population. United States data based upon the returns from a 10 per cent sample of death certificates received in vital statistics offices, as published in "Current Mortality Analysis," a monthly report of the National Office of Vital Statistics of the U. S. Public Health Service.

TABLE 2

Number of deaths and death rates from diabetes in geographic division; United States reporting area for the 10 per cent sample; January-June 1955, 1954 and 1953

Geographic Division	Death Rates per 100,000*			Number of Deaths*		
	1955	1954	1953	1955	1954	1953
U.S. reporting area	15.9	15.8	17.0	1,294	1,254	1,332
New England	18.6	18.1	18.2	92	88	87
Middle Atlantic	22.3	22.0	23.2	351	342	356
East North Central	18.5	19.3	21.1	303	310	333
West North Central	12.6	15.1	18.4	92	109	131
South Atlantic	12.4	13.0	14.0	144	148	156
East South Central	10.1	10.9	8.9	59	63	51
West South Central	14.0	10.4	13.6	109	80	103
Mountain	9.9	7.1	12.0	29	20	33
Pacific	12.8	11.4	10.2	115	94	82

*Excludes armed forces overseas.

Note: These data from the 10 per cent sample are subject to sampling error. The number of deaths, as given, does not cover the entire United States for each month but is limited by the completeness of the reporting area. The size of the reporting area is indicated by the footnote on page 7 of each monthly issue of the "Current Mortality Analysis."

Source: Data furnished by National Office of Vital Statistics of the U. S. Public Health Service.

differences reflect the variations in the incidence of respiratory diseases during the outbreaks last winter. Comparisons for the first half of 1953 and 1955 showed moderate reductions or very small increases generally. The only populous section to show a large increase between the two years was the Pacific Coast region. The rate for the country as a whole showed a decrease of 6 per cent. The early part of 1953 witnessed a much severer outbreak of respiratory diseases than occurred in 1955, but the geographical distribution of these outbreaks was not the same in the two years.

DIABETES MORTALITY IN CANADA, 1950-1953

Readers of this *Journal* both in the United States and Canada will be interested in recently published figures on mortality from diabetes in the ten provinces of Canada. The death rates for the period 1950-1953 for the country and for the several provinces are shown in table 3. For the country, the death rate from the disease has varied little during this period. In the two most populous provinces, the trends in this four-year period differed somewhat: The rate in Quebec showed little change, but the rate in Ontario has fluctuated rather widely but tended to fall.

TABLE 3

Mortality from diabetes mellitus in Canada by provinces, 1950-1953 (by place of residence)

Province	Death rates per 100,000				
	1950-1953	1953	1952	1951	1950
Canada	11.1	11.0	10.9	11.3	11.3
Newfoundland	4.9	4.2	4.3	5.8	5.1
Prince Edward Island	6.4	4.7	12.6	7.1	1.0
Nova Scotia	10.8	9.4	10.3	11.8	11.6
New Brunswick	9.8	10.6	10.6	10.1	7.8
Quebec	12.4	12.2	12.7	12.4	12.4
Ontario	11.9	11.6	11.1	12.7	12.3
Manitoba	9.3	10.4	9.1	8.8	8.9
Saskatchewan	9.1	8.9	10.0	7.7	9.7
Alberta	10.1	9.9	10.7	9.5	10.1
British Columbia	10.2	10.4	8.7	10.4	11.2

Source: Vital Statistics, Dominion Bureau of Statistics, Health and Welfare Division, Canada, Annual Reports 1950-1953.

Quebec and Ontario, in that order, had the highest average rate from diabetes for the four years and Newfoundland and Prince Edward Island had the lowest. The rates in the prairie provinces and the far west were somewhat below the average for the country. Unfortunately, detailed data needed to adjust the rates by provinces for differences in sex and age distribution of the population are not available. Such differences account for part of the variation in the rates shown. Per-capita income, relative abundance of medical personnel and facilities and other socio-economic factors significantly affect the level of mortality from the disease in the several provinces.

In Canada, as is generally true elsewhere, the death rate from diabetes among females is appreciably higher than among males (see table 4). At all ages combined the crude rate in 1953 among females exceeded that of males by 50 per cent. Up to age 45, however, the rates for males were almost uniformly higher than those for females; after that age, the situation was reversed. The greatest difference, relatively, was found at ages 55 to 64 where the female rate was double that for males. In both sexes the rates rose with increasing age to a maximum at ages 75 to 84.

TABLE 4

Mortality from diabetes mellitus in Canada by sex and age—1953

Age Period	Death Rates per 100,000		
	Total	Males	Females
All ages	11.0	8.8	13.2
Under 15	.5	.6	.4
15-24	1.3	1.2	1.4
25-34	2.1	2.5	1.7
35-44	2.8	3.2	2.4
45-54	8.2	7.0	9.4
55-64	32.1	21.2	43.6
65-74	68.1	53.0	84.3
75-84	127.2	103.7	149.8
85 and over	102.0	88.6	112.2

Source: Vital Statistics, Dominion Bureau of Statistics, Health and Welfare Division, Canada, 1953.

ANALYSIS OF MULTIPLE CAUSES OF DEATH

A primary aim in the procedures of death certification set up in connection with the *Sixth Revision of the International List of Causes of Death* was to obtain an increased degree of uniformity in classification in order to make possible more accurate and comprehensive comparisons between countries on causes of death. Nevertheless, differences between countries with respect to their medical resources and with respect to the points of view of their physicians are reflected in rather wide variations in the reported mortality rates from particular causes. It has been thought that some information of value might be elicited from analysis of multiple causes as reported on death certificates. This of itself, however, is greatly influenced by variations in frequency from one country to another in the proportion of certificates that bear reports of more than one cause of death statement. At the time the Sixth Revision was adopted it was recommended that tabula-

tions of multiple causes be made at intervals, preferably around the census year when the best and most accurate information with regard to the characteristics of the population by sex and age would be available. Because of the considerable amount of labor involved in making these multiple cause tables, relatively little has been done about it. Accordingly, a recent recommendation by the World Health Organization is that such tabulations be made on a limited scale, and specifically recommended were tabulations relating to diabetes and tuberculosis.

Some work along these lines based on special tabulations has been reported in these columns at various times. Such a tabulation was made on a 10 per cent sample of deaths registered in England and Wales during the first 6 months of 1951. In that sample, consisting of 32,631 deaths, diabetes was reported on 523 certificates. In 200 of the deaths, or less than 40 per cent of the total, it was the underlying or primary cause. In these cases, complications were frequently reported, but unfortunately, the published data do not indicate the number in which diabetes was certified as the sole cause. Even so, the complications reported on death certificates number 278, or 1.4 per death, based upon the total of 200 ascribed to diabetes. About two-thirds of these complications were cardiovascular. In

TABLE 6

Duration of life from onset to death among 2,897 deceased diabetics
Deaths between Jan. 1, 1950, and 1955*
Experience of Joslin Clinic, Boston, Massachusetts

a. Average—by age groups at onset

Age Groups at onset	Number of cases	Duration years
All Ages	2,897	16.0
0-9	81	20.8
10-19	163	20.3
20-39	448	22.2
40-59	1,465	16.4
60 and over	736	9.9
Unknown	4	—

b. Number and per cent of cases classified according to duration

Duration years	Number of cases	Per cent
All Cases	2,897	100.0
Less than 5	307	10.6
Less than 1	53	1.8
1	57	2.0
2	52	1.8
3	72	2.5
4	73	2.5
5-9	473	16.3
10-14	624	21.6
15-19	543	18.8
20 and over	946	32.7
Unknown	4	—

Average 16.0 Median 15.4

*Deaths reported through May 3, 1955.

TABLE 5

Diabetes as an underlying and contributory cause of death
Diseases or conditions reported as contributory to diabetes and to which diabetes was reported as contributory
Multiple cause of death analysis
England and Wales, 1951

Diabetes Primary Cause (200 Cases)		Diabetes Contributory Cause	
Complication or contributory condition	Number	Underlying cause	Number
Total complications reported	278	Total	323
Cardiovascular-renal	146*	Cardiovascular-renal	203
Cardiac	70	Cardiac	135
Coronary	23	Coronary	52
Vascular lesions	21	Vascular lesions	49
General arteriosclerosis	29	General arteriosclerosis	11
Nephritis and nephrosis	4	Nephritis and nephrosis	8
Gangrene (unspecified)	22		
Other diseases of nervous system†	19	Tuberculosis of respiratory system	16
Other diseases of circulatory system†	34	Influenza	21
		Pneumonia	20
Tuberculosis of respiratory system	1	Cancer (selected sites only)	11
Influenza	4	Other	52
Pneumonia	14		
Cancer, total	5		
Senility	14		
Other	41		

*Two or more of these complications are reported in some cases.

†Probably acute or minor conditions or symptoms. It is likely too that many of the cases with these conditions were reported to have chronic cardiovascular disorders and are counted in that group also.

Source: The Registrar General's Statistical Review of England and Wales for the year 1951. Her Majesty's Stationery Office, 1954.

22 cases, or 11 per cent of the 200 deaths, gangrene was mentioned, but this probably does not cover all cases so diagnosed. In about three-fifths of deaths where diabetes was a contributory cause, a cardiovascular disorder was reported as the underlying cause. Other diseases to which diabetes was frequently reported as contributory were influenza, pneumonia, tuberculosis and cancer (table 5).

DURATION OF LIFE WITH DIABETES

The duration of life from onset of diabetes to death has been tabulated for patients of the Joslin Clinic known to have died between Jan. 1, 1950, and May of 1955 (table 6, see page 404). The average duration, so defined, was 16.0 years at all ages and the median duration 15.4 years. In all age groups at onset up to age 40 years, the average exceeded 20 years; for those 60 and over it was about half that figure; at ages 40 to 59 it was 16.4 years.

In almost a third of the cases the duration of life from onset to death was 20 years or more. In only a little more than 10 per cent was it less than 5 years.

The Satiety Values of Specific Foods

This subject has been studied by Kestler, who classified foods according to their satiety value. It is interesting to note from the tables given by him that meat calls forth an amount of gastric secretion which is directly proportional to the amount eaten, whereas certain other foods, such as bread, potatoes and butter, when eaten in increased amounts do not excite a proportionate increase in gastric juice. This is explained by the fact that in the former instance the exciting agents are chemical—meat extractives—and that the stimulus exerted by them is directly proportional to their amount, while in the latter instance, the stimulus to secretion is dependent on psychic influences and therefore may be no greater after the ingestion of 100 gm. of bread than after the ingestion of 50 gm. . . . . Thus the great importance of meat as a food lies not only in its fuel value and in its ability to replace worn out structures, but also in its quality of calling forth great physiologic activity of the stomach, which in turn gives it great satiety value. It is well known that a meal which contains meat "sticks to the ribs" and lasts longest.

Next to meat in satiety value stands milk; the richer the milk the greater in this respect is its value. The satisfying quality of eggs depends somewhat on the cooking. Raw eggs leave the stomach much more rapidly than soft-boiled eggs, while those that are hard-boiled remain longest and call forth the greatest amount of secretion. Cooked eggs are to be preferred to raw eggs, not only because they are more easily digested, but also because their satiety value is greater. Fish is of much lower satiety value than meat or eggs, probably because fish yields less of the stimulating extractives than does meat. The same applies to oysters, but not to eel and other fish rich in fat.

The satiety value of bread is relatively low; it is still lower when toasted. The addition of butter, however, because of its high fat content, greatly enhances the staying qualities of the bread, which perhaps explains why buttered bread is preferred. Potatoes belong in the same category as bread, although in isodynamic quantities, the former are of definitely higher satiety value. This low rating of bread and potatoes, however, does not hold good under all circumstances, for when these foods are eaten with meat they have the power of increasing still further the satiety value of the meal.

Green vegetables such as spinach, lettuce and asparagus, also have relatively low satisfying values. Unlike bread and potatoes, they add little to the satiety value of meat. Likewise coarse articles which are entirely indigestible, such as bran and paraffin, remain in the stomach only a short time and have no satiety value.

Fats such as butter and olive oil, by retarding the emptying of the stomach, increase the satiety value of the meal. This quality of fat depends somewhat on its melting point and viscosity. The great satiety value of fat perhaps explains why a salad is more enjoyable when taken with an oil dressing.

The influence of sugar on the satiety value of the diet is important. This has been demonstrated by experiment as well as by experience. For instance, a test meal containing bouillon, meat, butter and potatoes was given twice, first without sugar and then with sugar. Without sugar the gastric secretion was 1,200 cc., and the evacuation time was three and a half hours; with sugar, the secretion was 1,288 cc., and the evacuation time eight hours. Therefore a meal to which something sweet has been added stays longer in the stomach and therefore has greater satiety value.

From the book *Nutrition and Diet in Health and Disease* by James S. McLester, M.D., and William J. Darby, M.D., Ph.D. Philadelphia, W. B. Saunders Co., 1952, 6th ed., pp. 130-31.

ABSTRACTS

Alpert, Samuel (*Veterans Administration, Regional Office, New York, N. Y.*): IMPAIRED GLUCOSE TOLERANCE, A CONSEQUENCE OF EXCESSIVE CARBOHYDRATE CONSUMPTION. Ann. Int. Med. *42*:927-31, April 1955.

The author reports a case of transient impairment of glucose tolerance resulting from excessive carbohydrate intake. He regards this phenomenon as one of exhaustion of pancreatic islet tissue, which may arise from excessive functional demand.

Andalón, Rodrigo; Martínez, César; and de Luna, Norberto (*Hosp. Civil "Dr. Pedro Martínez Pérez," Piedras Negras, Coahuila, Mexico*): LUMBAR SYMPATHECTOMY. El Médico *4*:19-22, February 1955.

In dealing with peripheral arteriosclerosis, the authors find that lumbar sympathectomy gave the best results in cases in which there was decreased peripheral pulsation in the lower extremities without trophic changes in the soft tissues. Diabetic patients showing peripheral vascular disease with trophic changes in the skin, toes, and toenails were less benefited by this surgical procedure.

A third group of patients showed osteoporotic changes and signs of ischemic neuritis in the lower extremities. In this group, complications such as nephrosclerosis and angina pectoris were frequent, and lumbar sympathectomy should be carefully evaluated. (Spanish)

Anderson, George E. (*Dept. of Med., State Univ. of New York Coll. of Med., New York, and Brooklyn Hosp., Brooklyn, N. Y.*): PRACTICAL METHOD OF REHABILITATION OF INSULIN FUNCTION IN DIABETES. New York J. Med. *54*:2167-74, Aug. 1, 1954.

A six-minute insulin-responsiveness test, utilizing glucagon-free insulin by vein, showed characteristic responses in both the obese adult type of diabetic and the juvenile type (272 curves) studied to date. The obese adult type of diabetic usually suffers predominantly from a "relative" deficiency of insulin; the juvenile type of diabetic, at any age, suffers predominantly from an "absolute" insufficiency of insulin. The author found that the obese adult type of diabetic, before adequate therapy, usually shows poor responsiveness or nonresponsiveness to glucagon-free insulin on the six-minute test. This nonresponsiveness or poor responsiveness to insulin could frequently be converted to normal responsiveness (in 80 per cent) by adequate therapy—a rehabilitation of insulin function. The juvenile type tended to be normally or even excessively responsive to glucagon-free insulin. With proper dietary measures, his overresponsiveness could frequently be stabilized. This improvement or rehabilitation was also measurable by the six-minute responsiveness test to glucagon-free insulin.

The implications and significance of the findings are discussed.

Andreani, G.; and Corti, L. (*Florence, Italy*): ALLERGY TO INSULIN: STATISTICAL STUDY OF 1,500 DIABETICS. Sett. med. *42*:345-52, June 30, 1954 (Abstr. from J.A.M.A. *157*:184, Jan. 8, 1955).

The occurrence of allergic reaction to insulin during the treatment of diabetes is rare. Local reactions, limited to the site of injection, are commoner than generalized reactions with diffuse, itchy urticaria; angioneurotic edema; gastro-intestinal disturbances; bronchial asthma; and other symptoms. Sometimes either type of reaction can be associated with resistance to insulin. Of a total of 1,522 diabetics who were using insulin, mild local reactions developed in 16 patients (1.05 per cent) and a marked generalized reaction to the drug occurred in three patients (0.2 per cent). The manifestations were so pronounced that insulin therapy had to be discontinued.

Azerad, E.: FREE DIET IN THE TREATMENT OF DIABETES. Semaine hôp. Paris *30*:1347, 1954 (Abstr. in Prensa méd. argent. *42*:282-84, Jan. 28, 1955).

The author favors the use of "free diet" for a diabetic patient with normal weight and without advancing complications, provided that frequent urinalyses are made to adjust the insulin requirements. (Spanish)

Bates, Margaret W.; Mayer, J.; and Nauss, Susan F. (*Dept. of Nutrition, Harvard Sch. of Pub. Health, Boston, Mass.*): FAT METABOLISM IN THREE FORMS OF EXPERIMENTAL OBESITY: ACETATE INCORPORATION. Am. J. Physiol. *180*:304-08, February 1955.

C^{14} carboxyl-labeled acetate was fed to three types of obese animals and their controls, obese-hyperglycemic mice, goldthioglucose obese mice, and rats with lesions in the hypothalamus. The C^{14} retention in carcass and liver lipids was measured when the animals were underfed and losing weight and when the weights were maintained. The obese-hyperglycemic mice and hypothalmic rats retain more C^{14} in carcass lipids than their controls when losing weight; the goldthioglucose obese mice retain the same amount as their controls. All obese animals retain more than their controls when their weights are maintained. Carcass fat content, strain, and

nutritional state were excluded as possible causes of the difference in C^{14} retention between obese and nonobese as well as between the obese groups when the animals were losing weight. These differences must be ascribed to dissimilar patterns of fat metabolism in the various types of obesity.

Bates, Margaret W.; Mayer, J.; and Nauss, Susan F. (*Dept. of Nutrition, Harvard Sch. of Pub. Health, Boston, Mass.*): FAT METABOLISM IN THREE FORMS OF EXPERIMENTAL OBESITY: FATTY ACID TURNOVER. Am. J. Physiol. *180*:309-12, February 1955.

Fatty acid turnover was measured in three forms of experimental obesity when the animals were gaining weight. The three forms of obesity studied were obese-hyperglycemic mice, goldthioglucose obese mice, and rats with hypothalamic lesions and their respective controls. This was done by feeding the animals C^{14} carboxyl-labeled palmitic acid and then measuring the decline in isotope content of carcass fat with time.

Both groups of obese mice mobilized significantly less fat daily than their controls. The amount of fat turned over daily was 50 to 60 per cent of the control value. The hypothalamic rats, on the average, mobilized considerably less fat daily than their controls. The absolute amount of fat turned over daily by the hypothalamic rats was of the order of 5 per cent of that found for the controls.

These results support the hypothesis that different types of obesities are characterized by different patterns of fat metabolism.

Bates, Margaret W.; Nauss, Susan F.; Hagman, Norma C.; and Mayer, J. (*Dept. of Nutrition, Harvard Sch. of Pub. Health, Boston, Mass.*): FAT METABOLISM IN THREE FORMS OF EXPERIMENTAL OBESITY: BODY COMPOSITION. Am. J. Physiol. *180*:301-03, February 1955.

As compared with controls of equal age, increased fat content accounts for more than 90 per cent of the increased weight of obese mice in three forms of experimental obesity: (a) hereditary obese-hyperglycemic, (b) goldthioglucose, and (c) hypothalamic. The fat accumulated in obesity is chemically similar to that of nonobese animals. The most striking differences observed were the lower protein content in the young obese-hyperglycemic mice and the greater body cholesterol content of the young and mature obese-hyperglycemic mice. The decreased protein content may be a reflection of decreased growth hormone secretion by the pituitary, secondary to hypersecretion of pancreatic alpha cells for which growth hormone appears to be trophic.

Benham, William D. (*Dept. of Neuropsychiatry, Walter Reed Army Hosp., Washington 12, D.C.*): NORADRENALIN IN ANAPHYLACTIC SHOCK FROM INSULIN; REPORT OF A CASE. Dis. Nerv. System *15*:317-18, October 1954.

The author presents the case of a 35-year-old woman who developed anaphylactic shock following 400 units of regular insulin given subcutaneously for insulin shock therapy. Four milligrams of noradrenalin were administered intravenously in 1 liter of 5 per cent glucose in water at a rate of 60 drops per minute with restoration of blood pressure. The infusion was gradually slowed until, in two hours, the blood pressure was maintained naturally.

Bessone, M.; and Miguez, J. G.: THE EXTERNAL PANCREATIC SECRETION AND ITS INSULIN CONTENT. Actas Bioquímicas *2*:49-52, November 1953.

There has been some interest in the past regarding the possible existence of insulin in the external secretion of the pancreas. Ten cubic centimeters of pancreatic secretion were diluted in water containing small equal quantities of hydrochloric acid and 95 per cent ethyl alcohol. The filtrate was redissolved, and successive purifications with alcohol and picric acid were made. Bio-assay in rabbits showed this preparation to have hypoglycemic activity manifested by a 27 per cent fall in blood sugar one hour after its administration. It is possible that this hypoglycemic activity is the result of insulin present in the pancreatic external secretion.

Bhattacharya, Gangagobinda (*Dept. of Physiol., Univ. Coll. of Science and Technol., Calcutta, India*): ON THE PROTECTION AGAINST ALLOXAN DIABETES BY HEXOSES. Science *120*:841-43, Nov. 19, 1954.

In studies upon rats with intravenous alloxan injection (40 mg. per kg.), the author reports that the simultaneous administration of d-glucose, d-mannose, or d-fructose in sufficient dosage protected against the subsequent development of diabetes. The following sugars, given orally before the alloxan (40 mg. per kg. intravenously), did not protect against diabetes: sucrose, lactose, d-xylose, d-arabinose, l-arabinose, d-sorbitol, d-mannitol, and sodium-gluconate. Maltose offered protection by the oral but not by the intravenous route. To furnish 100 per cent protection, the relative capacities of the sugars were glucose: mannose: fructose=100:50:15, based on the relative quantities necessary for this purpose.

These relative protective abilities correspond closely with the relative affinities for mammalian hexokinase. The author postulates a hexokinase inhibition theory of alloxan diabetogenic action with a competitive antago-

nism for the enzyme offering the basis for the protective action of the sugars. Study of the effect of alloxan on succinic oxidase gave no evidence indicating a direct reaction between hexose and alloxan. Support for the theory of competitive antagonism is offered by the fact that increasing the dose of alloxan overcame the protective action of glucose, and further increase in the dose of glucose again counteracted the effect of the alloxan.

Brentano, C. (*Berlin, Germany*): RESISTANCE TO INSULIN RESULTING FROM EXCESSIVE DOSES OF INSULIN: ITS TREATMENT WITH THIOURACIL COMPOUNDS. Ztschr. klin. Med. *152*:371-90, 1954 (Abstr. from J.A.M.A. *157*:684, Feb. 19, 1955).

The author believes that resistance to insulin may develop as a sequel of chronic excessive insulin dosage. Without change in the diet and without recognizable causes, glycosuria sometimes increases, and the physician increases the insulin dosage. Instead of responding to the higher insulin doses, the metabolic condition becomes constantly more unfavorable.

The resistance to insulin may be produced by excessive functioning of the thyroid; the adrenal cortical as well as other functions may likewise be involved. Insulin resistance after excessive insulin dosage may represent a counterregulation. The author claims that the administration of thiouracil preparations, particularly of phenylthiouracil, was effective in bringing about a normal response to insulin in a relatively short time.

Camerini, Dávalos, Rafael A.: CAPILLARY FRAGILITY AND DIABETIC VASCULOPATHY. Rev. Asoc. argent. dietol. *11*:89-93, July-December 1953.

Out of a group of 52 diabetic patients, 44.3 per cent were found to have a normal capillary resistance, whereas 55.7 per cent had an increased capillary fragility. There was no direct correlation between an increased capillary fragility and the presence of retinopathy, hypertension, and alterations in renal function. (Spanish)

Carbon, John A.; Blackwell, R. Quentin; Calandra, J. C.; and Fosdick, L. S. (*Chem. Dept., Northwestern Univ. Dental Sch., Chicago, Ill.*): THE INHIBITION OF ANAEROBIC GLYCOLYSIS BY SODIUM *N*-LAUROYL SARCOSINATE. Arch. Biochem. 55:356-64, April 1955.

Using brewers yeast, the authors show that sodium N-lauroyl sarcosinate is effective in reducing the rate of glycolysis and apparently stops the uptake of inorganic phosphorus from the medium. Hexokinase is strongly inhibited by this compound; aldolase, less so.

Chesrow, Eugene J.; and Bleyer, John M. (*Cook County Institutions, Oak Forest, and Cook County Hosp., Chicago, Ill.*): THE SYNDROME OF DIABETES MELLITUS IN PROGRESSIVE MUSCULAR DYSTROPHY. Geriatrics *10*: 132-36, March 1955.

Disturbed carbohydrate metabolism was found to be present in a 63-year-old man with progressive muscular dystrophy of long standing. This is believed to be due to muscle wasting, with resulting decreased ability to store glycogen in the muscular system.

Cohen, E. M. (*Pharmacol. Dept., Univ. of Leiden, Leiden, Netherlands*): PREVENTION OF ALLOXAN DIABETES IN THE RAT BY SHAM OPERATIONS OF THE ABDOMEN. Acta physiol. et pharmacol. neerl. *3*:232-37, May 1954.

Several authors showed that clamping of both kidneys or of the spleen during an injection of alloxan may decrease the incidence of diabetes in some animal species. The authors demonstrated that, during a subcutaneous injection of alloxan in the rat, either clamping of only the left renal pedicle or exposure of the intestines lowered the percentage of animals becoming diabetic as compared to unoperated controls. Laparotomy without exposure of the bowels did not decrease this percentage. Clamping of one kidney during an intravenous injection of alloxan did not significantly decrease the incidence of diabetes.

Constam, G. R.; Hochstrasser, P.; and vonSinner, F. (*Basel, Switzerland*): PROGNOSIS OF DIABETES MELLITUS. Schweiz. med. Wchnschr. *84*:1233-39, Oct. 30, 1954 (Abstr. from J.A.M.A. *157*:683-84, Feb. 19, 1955).

The authors believe that early and adequate treatment offers the best prospect for preventing late symptoms or for delaying their occurrence for many years and slowing down their course.

Daughaday, William H.; Larner, J.; and Houghton, Ellabeth (*Depts. of Med. and Biol. Chem., Washington Univ. Sch. of Med., St. Louis, Mo.*): THE RENAL EXCRETION OF INOSITOL BY NORMAL AND DIABETIC RATS. J. Clin. Invest. *33*:1075-80, August 1954.

Depancreatized and alloxan diabetic rats were found to excrete much more inositol in the urine than did normal rats. Whereas the inositol in the urine of normal rats was little influenced by dietary intake, that of diabetic rats was correlated directly with the amount of inositol ingested. Diabetic rats absorbed inositol faster from the gut than did normal rats. The average inositol level in the blood of diabetic rats after oral inositol was found to be slightly higher than that of normal rats, despite an increase in urinary excretion of inositol.

An active tubular reabsorption of inositol is postulated. The reabsorption of inositol was inhibited in diabetic rats, in rats with nondiabetic glycosuria, and in

phlorizin-treated rats. An osmotic diuresis produced by sodium chloride did not result in inosituria comparable to that found in diabetes. The authors conclude that the inosituria of diabetes mellitus can be attributed to an increase in the renal clearance of inositol produced by glycosuria.

Davis, Edward G., Jr. (*1001 W. Franklin St., Richmond, Va.*): INJECTION OF INSULIN. J.A.M.A. *157*: 268, Jan. 15, 1955.

Insulin should be given in at least 30 and preferably as many as 48 different sites in rotation. If rotation of injection sites is not practiced, irregular absorption may occur, with consequent poor control and unpredictable insulin shocks. There may also appear hypertrophy of the subcutaneous tissues or atrophy of subcutaneous fat.

Djin, Liem Oey Yam; Vlasblom, A. G.; and Cohen, E. M. (*Pharmacol. Dept., Univ. of Leiden, Leiden, Netherlands*): ON THE HYPERGLYCEMIC EFFECT OF ADRENALIN IN HYPOPHYSECTOMIZED RATS. Acta physiol. et pharmacol. neerl. *3*:252-56, May 1954.

Liver glycogen and plasma sugar have been estimated after injection of adrenalin in hypophysectomized and in intact rats. Control animals, intact and hypophysectomized, were given saline. It was shown that a normal glycogenolytic response after a subcutaneous injection of adrenalin can be obtained from hypophysectomized rats if depletion of liver glycogen stores is prevented by controlled feeding. It is concluded that the pituitary gland is not directly involved in the glycogenolytic action of adrenalin.

Editorial (*Tavistock Square, London, England*): SUCROSURIA. Brit. M. J. *1*:900-01, April 9, 1955.

The work of Moncrieff and Wilkinson (Acta Pediatrica *43*: Suppl. 100, p. 495, 1954) is quoted, wherein sucrosuria was found as a cause of marasmus in three infants. In addition, all three were mentally defective and had hiatus hernias. It is suggested that sucrosuria may be more common than realized.

Edwards, W. S.; Siegel, A.; and Bing, R. J. (*Depts. of Med., Surg., and Physiol., Med. Coll. of Alabama, Birmingham, Ala.*): STUDIES ON MYOCARDIAL METABOLISM. III. CORONARY BLOOD FLOW, MYOCARDIAL OXYGEN CONSUMPTION AND CARBOHYDRATE METABOLISM IN EXPERIMENTAL HEMORRHAGIC SHOCK. J. Clin. Invest. *32*:1646-61, December 1954.

Cardiac output, stroke volume, and coronary blood flow were found to be diminished during oligemic and normovolemic phase of hemorrhagic shock experimentally induced in dogs. As a result of diminished coronary flow, the myocardial oxygen usage was significantly reduced during both phases of shock. The myocardial oxygen extraction showed no significant change during the oligemic and normovolemic phase of shock. The coronary vascular resistance fell during the oligemic phase and increased during normovolemia. Cardiac efficiency declined during oligemia; there was no uniform change in cardiac efficiency after transfusion of blood.

Arterial concentrations of pyruvate and lactate were elevated during oligemic and normovolemic shock. The arterial glucose concentration, which had risen during oligemia, declined during normovolemia. The myocardial extraction of lactate was increased during hemorrhagic shock. In contrast, elevation of arterial blood glucose concentration did not result in an increase in myocardial glucose extraction. In some instances, glucose concentration in coronary venous blood exceeded that in arterial blood. Myocardial pyruvate extraction was diminished, and, frequently, the pyruvate concentration in coronary vein blood exceeded that in arterial blood.

These data suggest to the authors that myocardial ischemia, resulting from a diminution in coronary flow, can bring about specific metabolic changes in the heart muscle; as for example, destruction of cocarboxylase.

Eichler, O.; and Heinzel, J. (*Berlin, Germany*): RESULTS OF MANY YEARS OF CONSERVATIVE TREATMENT OF PERIPHERAL CIRCULATORY DISTURBANCES WITH HYDERGINE. Arch. klin. Chir. *278*:568-84, 1954. (Abstr. from J.A.M.A. *157*:474, Jan. 29, 1955).

Of the authors' 157 patients 72.5 per cent obtained either good or satisfactory results with early conservative Hydergine therapy, a method of treatment which assumes a favorable position among the various others for peripheral disturbances of circulation.

Elgee, Neil J.; Williams, Robert H.; and Lee, Norman D. (*Dept. of Med., Univ. of Washington Sch. of Med., Seattle, Wash.*): DISTRIBUTION AND DEGRADATION STUDIES WITH INSULIN-I^{131}. J. Clin. Invest. *33*:1252-60, September 1954.

Distribution studies of insulin labeled with radioactive iodine (I^{131}) in rats showed concentrations of radioactivity to be high in kidney and liver, low in red blood cells and brain, and intermediate in other tissues, including muscle. The distribution pattern was different from that of NaI^{131} and I^{131}-labeled human serum albumin. Perfusion and radioautographic studies showed that the renal radioactivity was bound in the convoluted tubules.

The concentrations of total and protein-precipitable radioactivity in rat blood and tissues were found to be maximal within fifteen minutes after intravenous insulin-I^{131} injection and thereafter fell, in general, at rapid

rates. Nonprotein-precipitable radioactivity, initially negligible, rapidly increased as the insulin-I^{131} was broken down. Fifty per cent of the I^{131} was in the urine in twenty-four hours, but only 1.7 per cent was protein-precipitable. Distribution studies in the human showed many similarities to those in the rat.

Faelli, C. (*Turin, Italy*): CLINICAL EXPERIENCE WITH AEROSOL INSULIN THERAPY. Minerva med. *45*:1238-42, Nov. 17, 1954 (Abstr. from J.A.M.A. *157*:857, March 5, 1955).

Twenty-one children in whom the condition was not too severe were chosen for a comparative study of the effects of the administration of 10, 20, and 30 units of insulin by subcutaneous injection and in aerosol. The author used crystalline insulin, which was aerosolized at the speed of one unit per minute. Four children received no benefit from the inhalation; ten were benefited; and in seven, the effects paralleled those obtained with the subcutaneous injections. Many factors including the insulin concentration and its rate of diffusion (this can be influenced by combination with hyaluronidase or substances that decrease its surface tension), can influence the absorption of insulin given in aerosol form. This limited experience suggests that insulin administration by aerosol offers possibilities of practical application, but the technical aspects of the method (apparatus, concentration, and doses) need to be perfected.

Farquhar, J. W. (*Dept. of Child Life and Health, Univ. of Edinburgh, Edinburgh, Scotland*): CONTROL OF THE BLOOD SUGAR LEVEL IN THE NEONATAL PERIOD. Arch. Dis. Childhood *29*:519-30, December 1954.

Serial studies of blood sugar and eosinophil count carried out in a group of thirty-two normal infants were undertaken in order to scrutinize most closely the hypothesis that, in a newborn baby (after the first few hours), there would be a rise in blood sugar and a fall in eosinophils. No such relationship was found. This failure may well be due to the unreliable index represented by the circulating eosinophils, whose day-to-day fluctuations have been shown to be so great that their mean values have little meaning. These statistical findings do not prove that the hypothesis is mistaken; it is stated only that no evidence in its support could be found.

Ferguson, Arthur W. (*Dept. of Child Health, Univ. of Bristol, Bristol, England*): THE USE OF THE INSULIN ZINC SUSPENSIONS IN DIABETIC CHILDREN. Arch. Dis. Childhood *29*:436-42, October 1954.

A study has been made of insulin zinc suspension (IZS) in 15 diabetic children. In 14 of the 15 children, it proved possible to obtain satisfactory control in the hospital with 1 daily injection of IZS. Fourteen of the children have been observed as outpatients; 12 have remained well stabilized, though changes in the dosage have been needed in 4. In 3 of the children, maintenance of control with IZS was poor. All 3 had previously proved particularly unstable. Four of the children were previously untreated, and all of these were eventually well controlled by IZS. Two of them were treated initially with IZS and responded well. In 9 children, blood sugar control with soluble insulin and with IZS was studied for comparison. The control obtainable with 1 daily injection of IZS was, in all of them, at least equal to that given by 2 injections of soluble insulin.

There has been no evidence of deterioration in the activity of IZS during the study, and no evident reactions have occurred at the sites of its injection. It is suggested that the majority of diabetic children could probably be satisfactorily controlled by a single daily injection of insulin zinc suspension.

Foà, Piero P.; Galansino, Giorgio; Weinstein, Harriett R.; and Magill, Alfred M. (*Dept. of Physiol. and Pharmacol., Chicago Med. Sch., Chicago, Ill.*): INFLUENCE OF PROLACTIN ON BLOOD SUGAR IN NORMAL AND DEPANCREATIZED DOGS. Am. J. Physiol. *180*:313-16, February 1955.

The first intravenous injection of prolactin in normal dogs causes hypoglycemia associated with a marked degranulation of the beta cells of the islets of Langerhans. Repeated intravenous injections of prolactin in normal dogs cause hyperglycemia, with partial recovery of the B granulations. In depancreatized dogs, hyperglycemia follows the first injection of prolactin. It is suggested that the first injection of prolactin may liberate preformed insulin from the pancreas and that subsequent injections may partially exhaust the beta cells, allowing an as yet unexplained hyperglycemic effect of prolactin to become manifest. This hyperglycemic effect cannot be explained entirely by the liberation of anti-insulin hormones of pituitary, adrenal, or pancreatic origin, since it occurs also after the removal of these glands.

Foreign Letters (*England*): ALDOSTERONE. J.A.M.A. *155*:1365-66, Aug. 7, 1954.

The suprarenal steroid electrocortin has been found to be closely related to corticosterone, differing from it in having an aldehyde group on carbon atom 18. For this reason it has been renamed aldosterone. Aldosterone is 25 to 30 times as active as desoxycorticosterone. Like desoxycorticosterone, it causes sodium and chloride retention and increased potassium excretion. Unlike de-

soxycorticosterone, it converts hypoglycemic glucose tolerance curves to normal.

Foreign Letters (*France*): DIABETES. J.A.M.A. *157*: 529, Feb. 5, 1955 (Report of a paper presented at a meeting of Med. Soc. of Paris Hosps. in June).

In addition to freedom from glycosuria maintenance of the blood sugar within normal limits is recommended, with the trial of different types of insulin if necessary to achieve these objectives.

Gamble, James L., Jr.; and Najjar, Victor A. (*Dept. of Pediat., Johns Hopkins Univ. Sch. of Med. and Johns Hopkins Hosp., Baltimore, Md.*): HEXOKINASE REVERSIBILITY MEASURED BY AN EXCHANGE REACTION USING C^{14}-LABELED GLUCOSE. Science *120*:1023-24, Dec. 17, 1954.

In the hexokinase reaction, adenosine triphosphate+glucose⇄glucose-hexophosphate+adenosine diphosphate. The authors report the initial demonstration of reversibility of the reaction, using glucose labeled with radioactive carbon to observe the exchange reaction, required catalytic quantities of either adenosine triphosphate or adenosine diphosphate.

Guimarães, José Ricardo Alves (*São Paulo, Brazil*): CONTRIBUTION TO THE STUDY OF CURABLE DIABETES. Rev. méd. brasil. *38*:27-32, January 1955.

The mechanism of production of diabetes by overfunction of pituitary, adrenal, and thyroid glands is discussed. Normoglycemia is the result of a concurrent activity of synergistic and antagonistic endocrine glands. A functional imbalance in the action of these glands would alter the blood sugar and cause hyperglycemia or hypoglycemia. (Portuguese)

Henríquez Inclán, E.; Pérez Alama, J.; Bueno, A.; Gómez Portugal, I.; Ushiyama, E.; and Oropeza, S. (*Gen. Hosp., Mexico, D. F., Mexico*): EXPERIMENTAL DIABETES INDUCED BY TEMPORARY ANOXIA OF THE PANCREAS FOLLOWING ADMINISTRATION OF DIABETOGENIC HORMONE. Medicina, México *35*:149-52, April 10, 1955.

Intravenous injection of one milligram of growth hormone in dogs produced a diabetic state. When ligation of the arterial celiac axis is performed for a period of time varying between 5 and 40 minutes, the diabetogenic effect of growth hormone increases a thousandfold in comparison with the dose used intravenously in animals without such ligation. As the anoxemic state of the pancreas after ligation of the celiac axis progresses in time from 5 to 45 minutes, an increasing hyperglycemia is observed. This suggests that pancreatic anoxemia due to vasoconstriction could play a role in the pathogenesis of diabetes. (Spanish)

de Jesús Macías, José; and Rodríguez, Rafael (*Hosp. of Diseases of Nutrition, Mexico, D.F., Mexico*): DIABETES AND TUBERCULOSIS. Rev. invest. clín. *6*:435-48, October-December 1954.

The mortality rate due to diabetes mellitus has increased 81.3 per cent in the last ten years in the Federal District and 49.9 per cent in Mexico as a whole, whereas the mortality rate for tuberculosis has varied little during the same period. Tuberculosis appears more frequently in poorly controlled diabetics; this was true in 28 of the 31 cases of this series. The decreased resistance to infections in poorly controlled diabetics possibly can be explained on the basis of a poor nutritional state, hyperglycemia, depletion of liver glycogen, and altered protein and fat metabolism. (Spanish)

Keeney, Arthur H.; and Barlow, Fred D. (*Section on Ophthalmology, Univ. of Louisville Sch. of Med., Louisville, Ky.*): SUPPLEMENTAL TESTOSTERONE AND ESTRONE IN ALLOXAN DIABETES OF THE RAT. A.M.A. Arch. Ophth. *53*:407-10, March 1955.

The Hotchkiss-McManus-Friedenwald staining technic for demonstration of retinal vascular patterns in whole-mount preparations is not currently adaptable to the albino rat eye because of the intense purple background staining, which obscures the finer divisions of the retinal vessels. India-ink injection preparations appear to produce detailed and consistent demonstrations of retinal vascular patterns in the albino rat. Serial sections with more familiar stains, such as hematoxylin and triosin, are still of great value in following histologic details through small specimens, as afforded by the rat eye. No significant differences could be found in the incidence or severity of retinal changes in alloxan diabetic rats of either sex used as controls or in those receiving supplemental estrone or testosterone. Histologically normal eyes were recovered in similar percentages from all groups of diabetic rats in this study. From these findings, it is concluded that neither testosterone nor estrone, administered in moderately large doses, as specified, over periods of 2 to 11 months, significantly affects the histology of the retina in the alloxan diabetic rat.

Kelly, H. G.; Rao, P. T.; and Jackson, R. L. (*Dept. of Pediat., State Univ. of Iowa Coll. of Med., Iowa City, Iowa*): INSULIN REQUIREMENTS OF CHILDREN WITH DIABETES MELLITUS MAINTAINED IN GOOD CONTROL. A.M.A. Am. J. Dis. Child. *89*:31-41, January 1955.

A study of the serial insulin requirements and growth of forty-eight well-controlled juvenile diabetic patients revealed a relationship between the changing insulin requirement and the growth of girls and boys. The age of onset of the disease did not influence materially the

insulin requirement. A knowledge of the insulin requirements and growth at varying age periods of well-controlled diabetic patients helps in the evaluation of the degree of hypoinsulinism of individual patients and in the prediction of insulin and nutritional requirements for maintaining good control of the disease and a normal growth pattern.

Kinsell, Laurance W.; Michaels, George D.; and Foreman, Nadine (*Inst. for Metabolic Res., Oakland, Calif.*): HIGH VEGETABLE FAT DIET IN DIABETICS WITH EXTENSIVE VASCULAR DISEASE. Geriatrics *10*:67-71, February 1955.

High vegetable lipid diets adequate in protein, vitamins, and minerals will produce a normal plasma cholesterol in diabetic patients and individuals with hypercholesterolemia. In a small group of juvenile diabetics with widespread vascular disease, there appeared to be beneficial changes in the ocular-vascular status. Some of the vascular disease, particularly the nephropathy, continued to progress.

Kleckner, Martin S.; Kark, Robert M.; Baker, Lyle A.; Chapman, A. Zerne; Kaplan, Ervin; and Moore, Thomas J. (*Dept. of Med., Northwestern Univ. Med. Sch.; Dept. of Med., Univ. of Illinois Coll. of Med., Chicago; Med. Serv., V.A. Hosp., Hines, Ill.*): CLINICAL FEATURES, PATHOLOGY, AND THERAPY OF HEMOCHROMATOSIS. J.A.M.A. *157*:1471-76, April 23, 1955.

The classic type of hemochromatosis, primary hemochromatosis, is a disease found almost exclusively in men during the fifth or sixth decade. An enlarged liver, diabetes mellitus, pigmentation of the skin (cutaneous melanosis), impotence, loss of body hair, or various combinations of these manifestations, are pertinent clinical findings. The treatment of primary and heredofamilial hemochromatosis consists of dietary therapy of cirrhosis, management of diabetes mellitus, and repeated phlebotomy with withdrawal of large amounts of blood.

Kochakian, Charles D.; and Dolphin, John (*Dept. of Physiol. and Vital Econ., Sch. of Med. and Dentistry, Univ. of Rochester, Rochester, N. Y., and Oklahoma Med. Res. Found., Oklahoma City, Okla.*): THE PROTEIN-ANABOLIC EFFECT OF TESTOSTERONE PROPIONATE IN THE HYPOTHYROID RAT. Am. J. Physiol. *180*: 317-20, February 1955.

Testosterone propionate stimulates a protein-anabolic effect in thiouracil and surgical hypothyroid castrated rats similar to that in the castrated rat. If the androgen is administered later than about 18 days after thyroidectomy, a marked decrease in food intake occurs. This is not evident in the thiouracil-treated rats.

Lipmann, Fritz (*Biochem. Res. Lab., Massachusetts Gen. Hosp. and Dept. of Biological Chemistry, Harvard Med. Sch., Boston, Mass.*): DEVELOPMENT OF THE ACETYLATION PROBLEM, A PERSONAL ACCOUNT. Science *120*: 855-65, Nov. 26, 1954.

The author describes, within the segment of his own work and interest, the biochemical discoveries and integration of concepts which led to the finding and identification of coenzyme A and the elaboration of its metabolic functions at the enzymatic level—work which led to the award of the Nobel prize in medicine and physiology.

Lipsky, S. R.; Alper, B. J.; Rubini, M. E.; Van Eck, W. F.; and Gordon, M. E. (*Dept. of Internal Med., Yale Univ. Sch. of Med., New Haven, and Veterans Administration Hosp., Newington, Conn.*): THE EFFECTS OF ALKALOSIS UPON KETONE BODY PRODUCTION AND CARBOHYDRATE METABOLISM IN MAN. J. Clin. Invest. *33*:1269-76, September 1954.

The administration of large amounts of acetate as the sodium salt to normal and diabetic subjects produced alkalosis comparable to that induced by equimolar solutions of sodium bicarbonate. In normal subjects, the authors found no changes in blood glucose following the infusion of acetate or bicarbonate. In contrast, the administration of sodium acetate to diabetic subjects caused depressions in the splanchnic glucose output and peripheral glucose concentration. These effects were found to be associated with simultaneous increase in splanchnic ketone production and peripheral blood ketones. Diabetics treated with bicarbonate usually showed similar changes in peripheral glucose and ketone levels. The effect of alkalosis per se on carbohydrate metabolism is discussed.

Mach, R. S.; Mach, E.; and Fabre, J. (*Paris, France*): ALDOSTERONE: BIOLOGICAL AND CLINICAL EFFECTS. Semaine hôp. Paris *31*:67-70, Jan. 6, 1955 (Abstr. from J.A.M.A. *157*:1584, April 23, 1955).

A summary is given concerning present knowledge of the effects of aldosterone on water and electrolyte metabolism, on carbohydrate metabolism, on the formed elements of the blood, and on inflammatory processes and its inhibitory action on the hypophysis. Aldosterone has been identified with the "sodium-retaining factor" that is absent from the urine of persons with hypoadrenocorticism and present in increased amounts in persons with lipoid nephrosis, congestive heart failure, and hepatic cirrhosis. It produces retention of sodium and chlorine and increases urinary excretion of potassium.

Maengwyn-Davies, Gertrude D.; Becker, Bernard; Rosen, Davis A.; and Friedenwald, Jonas S. (*Wilmer Ophthalmological Inst., Johns Hopkins Univ. Sch. of Med. and Johns Hopkins Hosp., Baltimore, Md.*): A COMPARI-

SON OF THE ACETYLATING CAPACITY OF NORMALS AND DIABETICS WITH AND WITHOUT RETINOPATHY. Bull. Johns Hopkins Hosp. *4*:150-53, April 1955.

Since it is known that, in the diabetic state, both the turnover and the production of high energy phosphate is below normal, and that diabetics are prone to deficiencies of vitamins, some of which function as coenzymes in the phosphorylating mechanism, it is possible to believe that some of the complications of diabetes may arise out of inadequate conversion of vitamins to their metabolically active forms.

The present study deals with the rate of excretion of one gram of sulfadiazine, the quantity of acetylated sulfadiazine being subsequently determined. Diabetics show an increased acetylation by this measurement. This indicates that there is no evidence of a deficiency of acetylation by the diabetic patients and, hence, suggests an adequate quantity of pantothenate does not exist.

No difference was found between diabetics with and diabetics without retinopathy in respect to acetylating capacity.

Marble, Alexander (*Joslin Clinic, Boston, Mass.*): DIABETIC NEPHROPATHY. J. Clin. Endocrinol. *15*:499-502, April 1955.

The author reviews the subject of diabetic nephropathy and his own experience with patients manifesting this complication. He concludes that in respect to no other complication of diabetes was the relationship of control more definite or more striking than in respect to nephropathy. This experience with diabetic nephropathy lends further support to the growing conviction that sequelae of long-term diabetes are related to the degree of control maintained over the years. Although many points of basic importance remain obscure, the physician is obligated to plan treatment and supervise management to provide the best degree of control attainable. With methods now available, ideal control is rarely possible. But, if the goal is not set high, the result secured is almost certain to be less satisfactory. The hazards of producing psychological trauma in patients by insistence on careful control have been overemphasized. The happy, well-adjusted, and useful life is entirely compatible with careful control in diabetic management.

Meyer, Richard J. (*Dept. of Med., Georgetown Univ. Hosp. and Georgetown Univ. Sch. of Med., Washington, D.C.*): THE MEDICAL SIGNIFICANCE OF LENTICULAR OPACITIES (CATARACT) BEFORE THE AGE OF FIFTY (CONCLUDED) WITH EMPHASIS ON THEIR OCCURRENCE IN SYSTEMIC DISORDERS. New England J. Med. *252*:665-72, April 21, 1955.

The author states that the type of cataract seen in diabetes falls into two groups: transient refraction changes and true diabetic cataract formation. Transient refraction changes (such as sudden myopia) are a very common initial sign of diabetes and seem to be related, in part, to changes in hydration of the lens. They are usually stabilized with control of the diabetes. True diabetic cataract, on the other hand, is quite rare; and although it may regress when diabetic control is promptly instituted, it can quite rapidly reach a mature, irreversible stage. The true diabetic cataract is most often encountered in juvenile diabetes that is severe and poorly controlled.

The lenticular changes seen in diabetes are fairly characteristic, consisting of snowflake, milk-white cortical opacities with subcapsular vacuoles and clefts, especially in the posterior region of the lens. The cataracts are often rapidly progressive, and complete bilateral opacification of the lens may occur in two or three weeks. Extremely rapid cataract formation (in one to three days) may take place in very young patients, especially when the diabetes is severe.

The author suggests that either glucose or galactose might have a direct toxic effect on the lens or that the cataract formation might be related to a metabolic deficiency set up by the high blood sugar level but not related to insulin lack per se. The exact part played by catabolism, acidosis, or loss of essential nutrients (failure of synthesis) in cataract formation in uncontrolled diabetes remains to be clarified.

Perloff, William H.; Lasché, Eunice M.; Nodine, John H.; Schneeberg, Norman G.; and Vieillard, Carol B. (*Endocrine Clin. and Med. Wards, Philadelphia Gen. Hosp. and Endocrine Dept., Temple Univ. Sch. of Med., Philadelphia, Pa.*): THE STARVATION STATE AND FUNCTIONAL HYPOPITUITARISM. J.A.M.A. *155*:1307-13, Aug. 7, 1954.

The value of the glucose tolerance test as a measure of adrenocortical function is based on the ability of the adrenal steroids to maintain the blood sugar level. In adrenal hypofunction, the glucose tolerance curve may simulate that of hypopituitarism or may resemble the curve of mild diabetes. Diets deficient in carbohydrate for even a few days may result in a diabetic glucose tolerance curve in normal persons. After one week of fasting, lowered pyruvate and lactate content of the blood suggests temporary inhibition of glucose oxidation. After one week of partial starvation with some glucose in the diet, however, a steep rise of blood sugar, followed by an excessive fall and a rise in pyruvate and lactate, indicates increased glucose oxidation with no gluconeogenesis. W. H. Chambers ("Undernutrition and

Carbohydrate Metabolism," *Physiol. Rev.* 18:248, 1938) concludes that partial inanition may result in the rapid removal of glucose by glucose-hungry tissues and a glycogen-depleted liver, whereas complete starvation appears to be associated with an inability of the tissues to burn carbohydrate.

M. L. Chakrabarty ("Blood Sugar Levels in Slow Starvation," *Lancet* 1:596, 1948) found that glucose tolerance curves of famine victims showed a slow rise for three hours, followed by a considerable fall. Flat curves have been reported in some cases of anorexia nervosa, whereas in others a diabetic-like curve has been observed, followed by a precipitous fall in some. The diabetic-like curve improved in one instance after a period of refeeding. Flat tolerance curves for orally administered dextrose, as well as precipitously falling tolerance curves for intravenously administered glucose, have been noted in sprue, so that this abnormality cannot be explained on the basis of decreased gastrointestinal absorption alone. It is evident, therefore, that the glucose tolerance curve is the result of such a complex combination of factors that, when dietary deficiencies play an important role, interpretation is often difficult.

The insulin tolerance test may also be used as a measure of adrenocortical function, because, when cortical activity is increased [as in adrenocortical hyperfunction (Cushing's syndrome)], the patient is usually insulin resistant; whereas when cortical function is low, the patient is hypersensitive to the action of insulin. In addition to the increased insulin sensitivity of the patient with adrenocortical hypofunction, which results in extremely low blood sugars, there is a delay in return to fasting values (hypoglycemia unresponsiveness). Unfortunately for the purposes of differential diagnosis, this factor may also be modified by diet. The hypoglycemia unresponsiveness observed in some cases of anorexia nervosa has been reported to be less marked than that of hypopituitary cachexia, and this has been suggested as a differential point in diagnosis. The authors' results do not confirm this opinion.

Polachek, Abraham A. (*Veterans Administration Hosp., Fort Howard, Md.*): STEROID DIABETES. Maryland M. J. 4:195-99, April 1955.

Steroid diabetes occurs in less than 1 per cent of patients under therapy with corticotropin or cortisone. It is almost always associated with latent diabetes or family susceptibility. Without such a history, its production is so rare that a case report is presented. When it does occur, steroid diabetes is usually mild and reversible and should be no bar to further therapy.

Queries and Minor Notes (*New York, N.Y.*): ACIDOSIS. J.A.M.A. 155:1457, Aug. 14, 1954.

Clinically, the most frequent type of acidosis encountered is metabolic, occurring in diabetes, nephritis, and starvation or a failure of the kidney to excrete anions as rapidly as they accumulate in the blood.

Acidosis leads to an increased excretion of the mineral cations sodium and potassium. Such losses of mineral cations from the body are additional factors in the development of dehydration, and, when the mineral cations are excreted as buffer salts, such as phosphates, they are an added cause of acidosis.

Ketonuria, or acetonuria, signifies an accumulation of beta-hydroxybutyric acid and acetoacetic acid in the body and merely denotes a condition in which the urine contains ketone bodies. This condition may or may not be associated with a state of acidosis. The presence of ketone bodies in the urine does not necessarily prove that acidosis is present.

If water and sodium chloride are supplied in adequate amounts, the kidney will in most instances regulate the retention of electrolytes and restore equilibrium to normal, whether the disturbance is acidosis or alkalosis.

Queries and Minor Notes (*New Bethlehem, Pa.*): DIABETES. J.A.M.A. 157:1357, April 9, 1955.

Anticoagulant therapy has not been reported to have any effect on insulin requirement in diabetic patients. This applies to the direct effects of the commonly used agents, such as heparin, bishydroxycoumarin, and ethyl biscoumacetate (Tromexan). Of course, any intolerance to one of these agents sufficient to interfere with dietary intake would, in turn, affect insulin requirement.

Queries and Minor Notes (*New York, N.Y.*): DIABETICS WHO UNDERGO OPERATIONS. J.A.M.A. 157: 873, March 5, 1955.

There are various plans of management of the diabetic patient undergoing operation. On the morning of operation, an infusion of 1,000 cc. of 5 per cent glucose in water is given intravenously in lieu of breakfast. At the same time, about half of the day's total dose of insulin is given subcutaneously. During the procedure, the surgeon gives such fluids as may be thought desirable by him, but usually no insulin need be, or should be, administered. Within a few hours after operation, another intravenous infusion of 5 per cent glucose is often given and, at the same time, the balance of the day's total dose of insulin is given subcutaneously. Because of the stress of the operation and the anesthesia, rarely will too much insulin be given, even though the total grams of carbohydrate taken are less than on the

usual day of normal diet.

It is not uncommon to encounter diabetic patients with a high renal threshold for sugar. This may reflect either a diminished glomerular filtration rate or an unusually efficient rate of tubular reabsorption. The first factor is probably of more importance, since one usually sees the condition in elderly persons, many of whom have evidence of diminished renal function. In such patients, more reliance must be placed on blood sugar determinations than on tests of the urine.

Queries and Minor Notes: GLYCOSURIA IN SERVICEMEN. J.A.M.A. *157*:1458, April 16, 1955.

Transient glycosuria should never be regarded lightly. Individuals with mild but genuine diabetes mellitus may have sugar in the urine only occasionally. The discovery of any glycosuria should be followed by a determination of the blood sugar two hours after an ordinary meal or by a glucose tolerance test. A blood sugar value above 140 mg. per 100 cc. of blood two hours after eating strongly suggests diabetes. Values below 100 mg. per 100 cc. eliminate that diagnosis for all practical purposes. Intermediate values call for a glucose tolerance test.

Queries and Minor Notes (*Bend, Ore.*): INFANT WHOSE MOTHER HAS DIABETES. J.A.M.A. *157*:99, Jan. 1, 1955.

If the mother is in a state of glycemic equilibrium, it is not necessary to give glucose to the child at birth. If large amounts of protamine zinc insulin or isophane (NPH) insulin have been administered to the mother shortly before delivery, the infant's blood sugar level may be so low that glucose would be necessary. For this reason it is well to estimate the child's blood sugar level at birth and 24 hours later, remembering that it is low even in normal infants. Feeding should begin after 12 to 24 hours of life. The first feeding may be 5 per cent dextrose in water. Later, a standard milk, water, and sugar formula of 17 cal. per ounce should be given.

Queries and Minor Notes (*Woodhull, Ill.*): INSULIN AND SUGAR. J.A.M.A. *157*:1356, April 9, 1955.

There is no quantitative relation between the amount of glucose and the dose of quickly-acting insulin. The earlier carbohydrate is administered in hypoglucemia, the more effective its action will be and the smaller the amount required. This may vary from 1 gm. when administered intravenously to 5 or 50 gm. when administered by mouth. In clinical diabetes, one cannot estimate the number of units of insulin required to change the blood sugar by 100 mg.

Queries and Minor Notes (*Jackson, Miss.*): POSTMORTEM BLOOD SUGAR. J.A.M.A. *157*:780, Feb. 26, 1955.

A postmortem blood sugar determination does not allow, in general, a conclusion as to the antemortem blood sugar level. A determination of the sugar content of the cerebrospinal fluid is of even more value than that of blood from the left side of the heart, because it is not subject to so many extraneous influences. Glucose values of 200 mg. per 100 cc. or more in the blood from the left side of the heart or spinal fluid about 10 hours after death are considered presumptive evidence of diabetes mellitus. Blood from the right side of the heart is valueless. Hypoglycemia as a cause of death cannot be confirmed unless the blood is examined within two hours of death.

Rawls, William B.; and Tichner, Jerome B. (*654 Madison Ave., N.Y.*): ANNULAR PANCREAS WITH DIABETES MELLITUS. New York J. Med. *54*:3110-12, Nov. 15, 1954.

A case of annular pancreas and associated diabetes mellitus which was extremely labile and difficult to control is reported. Following operation for resection of the annular pancreas and relief of the partial duodenal obstruction, the diabetes mellitus became much more manageable.

Rinehart, J. F.; Toreson, W. E.; and Abul-Haj, S. K. (*Dept. of Path., Univ. of Calif. Sch. of Med., San Francisco, Calif.*): HISTOCHEMICAL STUDIES OF THE HYALINE ISLETS OF DIABETES. Am. J. Med. *17*:124, July 1954. (Abstr. of paper presented at the 7th Annual Meeting of the Western Society for Clinical Research, Portland, Oregon, Jan. 29-30, 1954).

Although hyaline alteration of the islets of Langerhans is said to be found in approximately 40 per cent of cases of diabetes, the nature of the hyaline material is not understood. Using a colloidal iron staining technic, the authors found that the material reacts in the manner of a mucopolysaccharide. In the early phases, the mucinous material was found to lie at the periphery of the delicate capillaries of the islets. Increasing accumulation of this substance eventually obliterated the cells of the islets. It appeared to the authors that the hyaline mucoid material is derived from the endothelium rather than the epithelium. They believe that even minor accumulations of such material might constitute a significant barrier to the release of insulin.

Robillard, Rosario (*Clinique Médicale, Hôp. Saint-Luc, Montréal, Canada*): DEGENERATIVE COMPLICATIONS IN DIABETES. Union méd. Canada *84*:174-83, February 1955.

The author states that cardiovascular degenerative

complications are responsible for 75 per cent of deaths in diabetic patients. Duration of diabetes plays an important role in the incidence of arteriosclerotic lesions. While only 30 per cent of diabetic patients of less than 5 years' duration develop arteriosclerosis, 52 per cent show arteriosclerosis after 15 years, and 80 per cent of them, after 25 years. Coronary insufficiency due to arteriosclerosis often leads to myocardial infarction, and peripheral vascular disease due to arteriosclerosis leads to the frequently seen gangrenes. (French)

Rose, Clement; and Barron, John (*Saxondale Hosp., Radcliffe-on-Trent, Notts, England*): ANAPHYLACTIC SHOCK AS A COMPLICATION OF INSULIN COMA THERAPY. Brit. M. J. *1*:583-84, March 5, 1955.

The authors report the occurrence of anaphylactic shock in a 40-year-old man with schizophrenia receiving 160 units of soluble insulin intravenously in his tenth shock treatment. Treatments had been daily. Symptoms included shock, asthma, and gastroenteric disorder. He was successfully managed with adrenalin. Skin tests later were positive.

Runyan, John W., Jr.; Hurwitz, David; and Robbins, Stanley L. (*Albany Med. Coll., Albany, N.Y.; Boston City Hosp., Boston, Mass.; Boston Univ. Sch. of Med., Boston, Mass.*): EFFECT OF KIMMELSTEIL-WILSON SYNDROME ON INSULIN REQUIREMENTS IN DIABETES. New England J. Med. *252*:388-91, March 10, 1955.

The authors reviewed the clinical records of 375 autopsied cases with diabetes mellitus to explore further the circumstances leading to changes in insulin dosages during the course of this disease. Two selected groups of patients were compared, 54 with and 52 without Kimmelsteil-Wilson renal lesions.

Both amelioration and increased severity of the diabetes, as judged by changes in insulin dosage, occurred in patients without relation to their renal lesions. The over-all result of these changes in insulin dosage was a decrease of two units from the basal to the preterminal periods in both groups of patients. It is concluded that the alterations in insulin requirements are not causally related to the renal lesion. Evidence is presented that amelioration of the diabetes is often, but not invariably, associated with the clinical syndrome of Kimmelsteil and Wilson (i.e., edema, albuminuria, and hypertension), which occurs in patients both with and without the proved renal lesions. In patients in whom this syndrome is present, decreased intake of food may contribute greatly to an amelioration of the diabetes. Diabetic acidosis is not unusual, even in patients with advanced Kimmelsteil-Wilson renal lesions, but is uncommon in patients with the clinical syndrome of Kimmelsteil and Wilson. There is no evidence in this study to support the thesis of Zubrod, Eversole, and Dana that a specific type of diabetes, characterized by amelioration of the severity of the disease and infrequent occurrence of acidosis, is associated with the Kimmelsteil-Wilson renal lesions per se.

Saint, E. G. (*Sydney, Australia*): ACUTE PANCREATITIS. M. J. Australia *2*:536-43. (Abstr. from J.A.M.A. *157*: 281, Jan. 15, 1955).

It is postulated that the pancreatitis occurring in the obese, in diabetics, and in patients of middle age (among whom women predominate) may have its origin in disordered lipid metabolism and/or arteriosclerosis.

Savitt, Leonard E. (*1033 Gayley Ave., Los Angeles, Calif.*): FAVORABLE RESPONSE OF NECROBIOSIS LIPOIDICA DIABETICORUM TO HYDROCORTISONE SUSPENSION. A.M.A. Arch. Dermat. *71*:506, April 1955.

The author reports two lesions of necrobiosis lipoidica diabeticorum on the leg of a patient, which showed about 90 per cent improvement following injections of hydrocortisone into the lesions. Previous lesions in the same patient have responded readily to cortisone ointment.

Shimizu, Nobuo; and Inoue, Gyozaburo (*Dept. of Anat., Wakayama Med. Coll.*): HISTOCHEMICAL STUDIES ON THE BRAIN GLYCOGEN OF RABBITS AND ITS CHANGES DURING INSULIN HYPOGLYCEMIA. Medical Journal of Osaka University *3*:337-43, August 1952.

The brain glycogen of normal rabbits and of those affected by insulin hypoglycemia was examined histochemically. Most severe decrease of glycogen is observed in the cerebral cortex and striatum and somewhat less decrease in the cerebellum; whereas, few if any changes took place in other regions of the brain.

Sjöstrand, Torgny (*Dept. of Clin. Physiol., Karolinska Sjukhuset and ECG Lab., St. Erik Hosp., Stockholm, Sweden*): THE ELECTROCARDIOGRAM IN HYPOPOTASSEMIA. Acta. med. scandinav. *151*:73-83, Feb. 8, 1955.

A survey was made of the electrocardiograms in 21 cases of hypopotassemia. The cases were carefully selected to exclude electrocardiographic changes from any other cause. The electrocardiogram shows a depression of the T wave, which may continue to negative values. Within certain limits, there may be a direct relationship between the height of the T wave and the potassium concentration in the serum. The ST segment has a tendency to be depressed, in relation to the PQ level. The classical U wave was observed in most cases. The nature of the diastolic hypopotassemia potential is discussed.

Staub, A.; Behrens, Otto K.; Ellis, J. T.; and Kennedy, R. W. (*Lilly Res. Labs., Indianapolis, Ind.*): THE GLUCAGON CONTENT OF CRYSTALLINE INSULIN PREPARATIONS. J. Clin. Invest. 33:1629-33, December 1954.

The hyperglycemic factor content of some crystalline insulin samples was determined on a quantitative basis. The crystalline zinc-insulin preparations contained 0.3 to 0.5 per cent of the factor. The effect of glucagon on insulin preparations was discussed.

Taylor, J. S.: HYPOGLYCEMIA IN CHRONIC ALCOHOLISM. Brit. M. J. 1:648, March 12, 1955.

The author reports a patient with chronic alcoholism who developed two unexplained bouts of hypoglycemia. The first was diagnosed by the response to intravenous glucose. In the second bout, the blood sugar was 61 mg. per 100 cc. A glucose tolerance test was normal. He suggests that the fatty liver of alcoholism may have considerable glycogen depletion.

Teitelbaum, Philip; and Stellar, Eliot (*Dept. of Psychol., Johns Hopkins Univ., Baltimore, Md.*): RECOVERY FROM THE FAILURE TO EAT PRODUCED BY HYPOTHALAMIC LESIONS. Science 120:894-95, Nov. 26, 1954.

The authors confirm Brobeck's report that stereotaxic-produced lesions of the lateral hypothalamus can cause rats to refuse to eat and starve to death. Ventromedial lesions at the same level produce hyperphagia. Administration of a nutritive-fluid diet by stomach tube postoperatively was followed by recovered eating and drinking behavior within 6 to 65 days, marked by stages of accepting evaporated milk or evaporated milk and milk chocolate, then water, and finally regular laboratory food. The time spent in each of these stages of recovery varied greatly among individual animals, but the sequence was almost invariable.

Thomas, Caroline Bedell; and Cohen, Bernice Hirschhorn (*Johns Hopkins Univ. Sch. of Med., Baltimore, Md.*): THE FAMILIAL OCCURRENCE OF HYPERTENSION AND CORONARY ARTERY DISEASE, WITH OBSERVATIONS CONCERNING OBESITY AND DIABETES. Ann. Int. Med. 42:90-127, January 1955.

The prevalence of hypertension, coronary disease, obesity, and diabetes among the parents, grandparents, aunts, and uncles of 266 medical students has been determined. The incidence of hypertension tended to be higher among females than in males in comparable groups. Coronary artery disease occurred more often among males than among females; this difference was more pronounced in the parents' generation. Of the parents, 12.2 per cent were obese; of the grandparents, 9.3 per cent were likewise affected. Diabetes was the least prevalent disorder, with an incidence rate of 2.4 per cent in parents and 4.1 per cent in grandparents. Combinations of two or more disorders affecting the same individual occurred more frequently among both parents and grandparents than might be expected by chance alone. The combinations of hypertension in coronary artery disease and hypertension in obesity were most frequent. A study of the incidence of the four disorders in siblings of affected and nonaffected parents revealed that: (a) Hypertension was three times as frequent in siblings of hypertensives as in siblings of normotensives, (b) coronary artery disease was almost four times commoner in siblings of individuals with coronary artery disease than in siblings of parents without it, (c) the siblings of obese parents had four times as much incidence of obesity as those of nonobese parents, and (d) diabetes was eight times as common among siblings of diabetic persons as among siblings of nondiabetic persons. The incidences of the various disorders in two successive generations were analyzed by comparing their prevalence among offspring of matings where both, one, or neither of the parents was affected. The genetic implications of the findings are discussed.

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de Venanzi, Francisco; Agüero, Oscar; and Roche, Marcel (*Inst. de Investigaciones Méd., Fundación Luis Roche, Plaza Morelos, Caracas, Venezuela*): CHANGES IN BLOOD SUGAR AND SERUM INORGANIC PHOSPHORUS AFTER DEXTROSE OR INSULIN ADMINISTRATION IN PREGNANCY. Acta physiol. latinoam. 4:185-89, 1954.

Changes in blood sugar and serum inorganic phosphorus were measured before and 15, 30, 45, and 60 minutes after the intravenous injection of dextrose (0.5 gm. per kg. of body weight) in a group of 28 women in the seventh to ninth months of pregnancy and in a group of 20 nonpregnant women of comparable age. A similar study was performed after the intravenous injection of 0.1 units per kg. of body weight of insulin in 19 pregnant women in the seventh to ninth month and in 37 nonpregnant women. A significantly greater increase in blood sugar and a lesser decrease in serum inorganic phosphorus following dextrose were found in the pregnant group. The blood sugar and serum inorganic phosphorus fall following insulin, was significantly lesser in the pregnant group as compared with the nonpregnant group.

Warren, Joel; Ziherl, Frank A.; Kish, Arthur W.; and Ziherl, Louis A. (*Walter Reed Army Med. Center, Washington, D.C., and Cleveland, Ohio*): LARGE-SCALE ADMINISTRATION OF VACCINES BY MEANS OF AN AUTOMATIC JET INJECTION SYRINGE. J.A.M.A. 157: 633-37, Feb. 19, 1955.

A multiple-dose, automatic jet injection syringe and pump and a single-dose, manually operated jet injection syringe are described for the administration of insulin, antibiotics, anesthetics, and vaccines. The units available at present are the property of the armed services and are for use solely for research and development.

Weber, George; and Cantero, Antonio (*Montreal Cancer Inst., Res. Lab., Notre Dame Hosp., Montreal, Quebec, Canada*): GLUCOSE-6-PHOSPHATASE STUDIES IN FASTING. Science *120*:851-52, Nov. 19, 1954.

The authors report an increase of glucose-hexophatase in fasting mice and rats. This increase may be considered as a physiological adaptive change to the stress of fasting, during which the glycogen stores are converted into glucose and depleted.

Wick, Arne N.; and Drury, Douglas R. (*Scripps Metabolic Clin., La Jolla, and Univ. of Southern Calif., Los Angeles, Calif.*): METABOLISM OF HEXOSES IN THE BODY. Am. J. Med. *17*:103, July 1954. (Abstr. of paper presented at the 7th Annual Meeting of the Western Society for Clinical Research, Portland, Oregon, Jan. 29-30, 1954).

According to the authors, the four common hexoses, glucose, fructose, galactose, and mannose, are handled by the extrahepatic tissues in various ways, which in some cases are influenced by insulin. Glucose, galactose, and mannose can enter the extrahepatic cells at a slow rate, which can be markedly accelerated by insulin. Glucose and mannose can be oxidized by the intracellular enzyme system, and their rate of oxidation is increased by insulin. The intracellular enzyme system has little, if any, capacity to oxidize galactose, although insulin accelerates its intracellular transfer. Fructose does not enter the extrahepatic cells to any measurable degree and is not changed by insulin. Consequently, the authors state, fructose is not oxidized by the extrahepatic cells. Other hexoses and related compounds react like fructose.

The treatment of hexoses by the liver is said to be altogether different. All of the common hexoses and related compounds seem to be able to enter the liver cells even without the mediation of insulin. Here, fructose as well as mannose can be oxidized. Preliminary work indicated to the authors that other hexoses will enter and may be used by the liver cells, even in the diabetic animal.

Wilbur, Dwight L. (*Stanford Univ. Sch. of Med., San Francisco, Calif.*): CARCINOMA OF THE PANCREAS. Mod. Med. *23*:75-83, May 1, 1955.

The author reviews various aspects of carcinoma of the pancreas with special reference to symptoms, signs, pathologic features, laboratory diagnosis, roentgenographic findings, and other diagnostic methods. The most important point to be decided when the diagnosis of pancreatic carcinoma seems established clinically, or when it is strongly suspected, is whether surgical exploration should be undertaken. In some cases, a lesion which may be amenable to surgical treatment may be found, and great physical and psychological relief to the patient may be obtained, even though length of life is unaltered. In some instances, it may be possible to remove the lesion.

Wrenshall, Gerald A.; and Bogoch, A. (*Banting & Best Dept. of Med. Research & Dept. of Path., Univ. of Toronto, Can.*): THE WEIGHT AND EXTRACTABLE INSULIN OF THE PANCREAS IN ADULT NONDIABETIC MAN. J. Clin. Endocrinol. *15*:435, April 1955.

The existence of an inverse correlation between the amount of extractable insulin per unit weight of pancreas and the total weight of the pancreas in adult human subjects has been demonstrated. Such a correlation, combined with the finding that the total weight of the pancreas is widely variable in man, indicates that, in man, the extractable insulin per gram of pancreas cannot be considered to represent a characteristic constant.

Yochem, Donald E. (*246 N. High St., Columbus, Ohio*): INSULIN SYRINGE CONTROL. J.A.M.A. *157*: 1610, April 30, 1955.

The instrument described will accurately control the amount of insulin that is drawn into the syringe. This instrument consists of a clasp and stop that are readily adaptable to the syringe barrel, a gauge piece that can be easily attached to or removed from the plunger head, and a small setscrew mounting. This instrument is especially useful to those who are afflicted with blindness or defective vision or who for other reasons experience difficulty with preinjection procedures.

EDITORIALS

PROGRESS REPORT ON LENTE INSULIN

A considerable sum of experience in the use of lente insulin ("insulin-zinc suspension") has now been reported by various workers in this country and abroad. It is well known as another depot insulin with timing of action intermediate between that of solutions of the hormone at one extreme and that of protamine zinc insulin at the other. It may be classed, therefore, with the commonly used mixtures of insulin and protamine zinc insulin, globin insulin, and isophane (NPH) insulin. It differs from those insulins chiefly in the fact that its insulin is precipitated by zinc in an acetate buffered solution. Thus, it contains no protein except insulin itself. Like protamine and NPH insulins it is suspended in a neutral vehicle and, like all depot insulins, it depends for its retarded action on the fact that insulin is released more slowly from subcutaneous deposits of the suspension and is more slowly absorbed than ordinary solutions of the hormone.

As marketed here, in Great Britain, Australia, Denmark, and most Latin American countries, lente insulin is a mixture of insoluble amorphous insulin, with rapid action only a little slower than insulin in solution (30 per cent), and crystals with slow action similar to that of protamine zinc insulin (70 per cent). Only the mixture is commercially available here, whereas its individual components ("semilente" and "ultralente") are also available abroad for modification towards faster and slower action, respectively, when needed.

Recent reports by various observers of clinical experience in a total of some 2,000 diabetic patients now provide a fairly clear picture of the probable advantages and disadvantages of this newest of the insulin modifications. There is no doubt of its intermediate action, not radically different from globin and NPH insulins.[1] The lente mixture in the proportion of 30 to 70 as marketed seems to fit the needs of fully 80 per cent of all patients when given in one dose daily. The minority in which it is not suitable as prepared are about equally divided between those requiring more rapid action and more slow action.[2, 3] In this country such modification can be accomplished only by the use of other insulins. Appreciable acceleration of action is possible by the addition of crystalline insulin.[4] Up to equal parts (unmixed) can be added to the syringe without change in the lente fraction provided the injection is made promptly.[4] Slowing of action is not feasible here. When that is necessary it is probably wise to use one of the older preparations. Occasionally burning is present on injection[5] and local allergic reactions are not much more infrequent than with other modifications.[3]

On transfer from older insulins to lente a behavior that is not uncommon with other depot insulins may be observed. A substantial number of patients have obtained such a weak or slow insulin effect that ketosis has occurred and emergency use of insulin in solution required.[2, 3] In some cases during an intercurrent infection it has been difficult to increase the dosage of lente insulin rapidly enough to keep pace with the demand.[2, 3] This effect should not be counted as a fault of lente insulin since it may occur with other depot modified insulins.

In retrospect, it seems probable that if the insulin-zinc suspensions had been discovered fifteen or twenty years ago, other intermediate-acting insulins might never

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[1] Marble, Alexander: Discussion of (4) and (5) below.

[2] Stowers, J. M., and Nabarro, J. D. N.: Clinical experience of the insulin zinc suspensions. Brit. M. J. Jan. 8, 1955, pp. 68-70.

[3] Gurling, K. J.; Robertson, J. A.; Whittaker, H.; Oakley, W.; and Lawrence, R. D.: Treatment of diabetes mellitus with insulin zinc suspension. Brit. M. J. Jan. 8, 1955, pp. 71-74.

[4] Hallas-Moller, K.: The lente insulins (to be published).

[5] Haunz, E. A.: Lente insulin: clinical evaluation in 109 diabetic patients (paper presented at the Fifteenth Annual Meeting of the American Diabetes Association, Atlantic City, N. J., June 5, 1955).

[6] Colwell, Arthur A.: Insulin-zinc suspensions (editorial). Diabetes 3:162-63, March-April 1954.

have been developed and problems of selection not have been presented. Their introduction now, however, adds to the complexity of the insulin situation. As suggested in a previous editorial review[6] the problem might become more simple instead if other depot insulins could be dropped from the market and the amorphous and crystalline insulin-zinc suspensions added. Otherwise it seems to this reviewer that little of practical importance has been gained. Since lente is the only depot insulin available which contains no foreign protein, it seems reasonable to hope that it might replace the others in time. It and its components seem to be capable of serving all necessary functions of depot insulins.

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SIR HENRY DALE'S CONTRIBUTION TO THE THERAPY OF DIABETES

In early June, the *British Medical Journal* published a series of four articles to celebrate the eightieth birthday of Sir Henry Dale. These articles were contributed by Lord Adrian, Master of Trinity College, Cambridge, Dr. Otto Loewi, Foreign Member of the Royal Society, Dr. J. H. Burn, Professor of Pharmacology, University of Oxford, and Dr. Herbert S. Gasser of the Rockefeller Institute for Medical Research. All four of these distinguished scientists paid tribute to the achievements of Sir Henry as an outstanding leader in research embracing the fields of anatomy, physiology, pharmacology, and clinical therapeutics.

The place of Sir Henry Dale in the scientific world is indicated by positions which he has held in his native country, such as Director of the National Institute for Medical Research and President of the Royal Society, and also by the long list of honorary memberships in foreign scientific societies and academies. Members of the American Diabetes Association will recall with gratification that he was the Banting Lecturer at the Annual Meeting of the Association in 1954 and a recipient of the Banting Medal on that occasion.

In the evaluation of Sir Henry's contribution to therapeutics, Professor Burn reviewed his activities at the time of the introduction of insulin.* His efforts to develop the production of insulin in Britain and his contribution to international standardization were described in the following terms:

> When Banting and Best announced the discovery of insulin and Macleod and Collip were assisting them to devise a method of preparing solutions for therapeutic use, Dale, with H. W. Dudley as his companion, visited Toronto to learn at firsthand of the progress of the work. (The information which they obtained on) this visit and the work which followed it (on their return home) enabled insulin to be made available in Britain in the shortest possible time as an agent which from the first was of nearly uniform potency.
>
> The situation was full of dangers. The manufacture of a product like insulin was new to pharmaceutical firms in every country, and it seemed too great an adventure for any single firm in Britain. It involved the preparation of an unstable substance in sufficiently purified form for subcutaneous injection, from a tissue rich in an enzyme which could destroy the insulin and which was full of other material. The preparation of insulin had defeated many who had attempted it on a small scale. What was now needed was a large-scale process which could be relied upon to produce insulin with regularity and at reasonable cost. This had to be accomplished with little guidance from previous experience of other tissues. For various reasons Dale sought to persuade the manufacturers who were interested to combine their resources, and as a result the two firms, Allen and Hanburys, and British Drug Houses, united to produce the AB brand. Much work was carried out by Dudley at the National Institute which enabled him to obtain insulin as a picrate, and in this way assistance was given in devising a commercial process. Frequent consultations between Dale, Dudley, and F. H. Carr greatly facilitated large-scale production.
>
> Still more important, however, was the solution to the problem of standardization, which from the first constituted a serious obstacle to progress in purification. It was studied intensively under Dale's direction. The Toronto workers from the first attempted to measure insulin in terms of a rabbit unit, the definition of which was continually modified in the attempt to make such a unit satisfactory. Difficulty arose from the fact that the injection of the same amount of insulin into different rabbits, even when these were of the same sex and of similar weight, caused a fall of blood sugar which differed in magnitude in different animals. The measurement of the hypoglycemia in different rabbits took considerable time, and for many months it was not obvious whether all the variation in the response of different animals could be overcome.
>
> Dale's own view from the first was that the method of standardization could not succeed if it was to depend on a rabbit unit, and yet it was essential that the method should be comparative, each preparation of insulin being tested in comparison with a standard preparation to determine the difference between them. This was the basis of Ehrlich's method of standardizing diphtheria antitoxin. Using this as a guiding principle, H. P. Marks, working under Dale's direction, finally arrived at an expression of the hypoglycemic effect on a series of rabbits in terms of the mean effect in the group. This constituted an important advance which had far-reaching consequences. When a given dose of one preparation was injected into several rabbits the hypoglycemic reaction of each rabbit differed, as had been pointed out. At that time the question seemed to be which

*Burn, J. H.: Sir Henry Dale's contribution to therapeutics. Brit. Med. Journal 1357-59, June 4, 1955.

of the different responses must be regarded as the correct one. A revolution of thinking was required before it was realized that all of the responses must be taken into account, and that the correct response was the mean of these very varying responses. Once this had been grasped, it was possible to determine a "dose effect" curve for insulin; that is to say, to determine for each of the series of doses of insulin the mean hypoglycemic response in several animals.

At this stage a firm basis for insulin standardization had been laid down; it was carried out as a comparison of an unknown sample with the preparations specially kept for use as a standard, so that the potency of the unknown sample could be expressed in terms of the standard. The unknown might be four-fifths of the standard or it might be one-and-one-half times the standard; the number of units the unknown contained was then determined by the number of units arbitrarily given to a certain weight of the standard. If it was decided to say that the standard contained 8 units of 1 mg., then it followed that if the unknown was four-fifths of the standard, the unknown must contain 6.4 units per mg.

This procedure today may seem simple and obvious, but in 1923 and 1924 it was entirely new for a substance such as insulin. The success achieved had a very wide influence on the biological standardization of many other substances. Moreover, it came at a time when the establishment of international standards had been under consideration and provided a compelling reason for international agreement. At the International Physiological Congress in Edinburgh in 1923, Dale, Magnus, and others had considered the question of having standard preparations of various kinds, Magnus being especially concerned with the standard preparation of digitalis. As an outcome the Health Organization of the League of Nations arranged a conference in Geneva in 1925, of which Dale was the Chairman. At that meeting, international standards were agreed upon by the representatives of several countries for insulin, pituitary (posterior lobe) extract, neoarsphenamine, sulpharsphenamine, and for digitalis. This was a great achievement which was based on the careful organization of experimental work in different countries beforehand, and led to close and friendly relations between all the workers concerned. It meant, for example, that in the case of insulin, that a uniform system of measuring its potency was adopted throughout the world within four years of its discovery. Had Dale not succeeded in persuading the other members to adopt the comparative method of standardization, the meaning of "one unit of insulin" might well have remained obscure and the potency of different samples might have shown wide variation for many years.

So successful was the Geneva Conference of 1925 that later conferences in 1928, 1934, 1935, and 1938 extended the list of substances for which international standards were provided almost as a matter of course. Since the second World War, work was continued under the World Health Organization and the number of international standard preparations has reached fifty, with another fifty under consideration. How great a contribution this has been to therapeutics throughout the world it is quite impossible to indicate or measure. It is very largely due to Dale's skillful persuasion that instead of confusion there is order and cooperation in a field where national prejudices are sometimes just as capable of preventing agreement as in politics generally.

A study of the above narrative throws light on the history of insulin and indicates how its discovery and introduction into everyday therapeutics had an important influence on the usage of other therapeutic agents throughout the world. It also illustrates the good judgment and practical thinking of Sir Henry Dale.

A Definition of Diabetes Mellitus

Diabetes mellitus is a chronic disease manifested by multiple disturbances in the metabolic processes of the body and is due to an insufficient supply of endogenous insulin. Furthermore, it lends itself to control by administration of insulin but is rarely if ever cured. The greatest apparent disturbance caused by this disease is in the utilization of carbohydrate, though the metabolism of fat and protein, and, indeed, the total food metabolism is affected. An insufficient secretion of insulin by the pancreatic islets of Langerhans, no matter what the cause, will precipitate the clinical syndrome of diabetes mellitus. Diabetes is not, however, as simple as this would make it appear. There is much convincing evidence that the reduction of insulin production is secondary to disturbances in other, but closely related, endocrine glands. Of these the diabetogenic influences of the anterior lobe of the hypophysis, and the adrenal glands are of outstanding importance. In contrast, the extent of the effect of the thyroid gland on the pancreas is not great. In some instances it seems that the insulin insufficiency is relative and not absolute; that there actually may be a normal amount of insulin produced but that its effect is neutralized to a greater or lesser degree by some antagonist. There can be no doubt that an insulin antagonist possessing an opposing physiologic action or a chemical neutralizing agent, exists in some instances.

By Garfield G. Duncan, M.D., in *Diseases of Metabolism,* edited by Garfield G. Duncan, M.D., Philadelphia, W. B. Saunders Co., 3rd ed., p. 775.

Adolf Magnus-Levy
1865-1955

Martin G. Goldner, M.D., New York*

Dr. Adolf Magnus-Levy died on Feb. 5, 1955, at the age of almost ninety years. Thus came to an end the life of an unusual man and an outstanding scientist. In the words of his old friend, Dr. Elliott P. Joslin of Boston, "he represented the acme of the closing days of the fabulous period of German medicine in the last century." His contributions indeed were highlights even in that era which was filled with great achievements in scientific medicine.

Magnus-Levy was one of the few men of the last century who initiated functional thinking and metabolic investigation in clinical medicine. At a time when tracer isotopes were not yet available, balance studies were largely limited to studies of intake and output and were, in Claude Bernard's words, "not much more reliable than if one attempted to learn something about a household by checking the food delivered at the entrance door and analyzing the smoke coming out of the chimney." Nevertheless, it is remarkable that the accuracy of many of the early metabolic researches and particularly those of Magnus-Levy remained unchallenged. He applied the study of energy exchange to the clinic, introduced and defined the Grundunsatz—the BMR—and studied it in health and disease with such thoroughness that almost a generation later another of his numerous friends in this country, Dr. Eugene F. DuBois, said that "Magnus-Levy had stated in 1897 clearly almost all the important facts about (energy) metabolism in disease . . . leaving little of importance for the workers of the next few decades." It was also he who demonstrated the metabolic action of the thyroid hormone and who brought to a successful conclusion the studies of diabetic coma by Naunyn's school. Moreover, he was one of the first to investigate the metabolism of electrolytes, and he presented such accurate chemical methods for their determination that the American physiologist Hemmeter sent his analyses from Baltimore to Berlin and sought his advice because, as he stated in one of his papers, "Magnus-Levy's work on the content of human organs on Cl, Ca, Mg, Fe, as well as H_2O and proteins belongs to the best which has been published as yet." Finally, he made important and still basic contributions to the enigma of multiple myeloma, amyloidosis, and the Bence-Jones protein.

It is a most significant indication of his talent and ingenuity, his resourcefulness and endurance that he made all these achievements singlehanded, working almost alone, without a staff of assistants and technicians, without public funds and most of the time without any official position at a university or a research institute, while supporting his family out of his own means and his private medical practice. Only during the three years of his assistantship under Naunyn in Strassburg from 1897 to 1901, which were in many respects the happiest of his earlier life, did he belong to a university staff. Naunyn, whom he admired as his master and who held him in great friendship, probably because of the similarity of the character of the two men, did not consider him merely as his student but said that "Magnus-Levy came to me as a mature man." He was already an accomplished investigator.

The importance of Magnus-Levy's career is greater than the sum of all his individual achievements. Long after "The Heroic Age of German Medicine," (as he had called that period in an historical paper of later days) had come to its decline, he remained the guardian of its heritage, recognized with respect and awe. For almost a generation afterward he was the personification of this period. Like a prophet of the Old Testament, he watched with devotion and faithfulness, conviction and honesty over its tradition, and castigated whenever and wherever he felt that the principles of "science for the sake of science" were violated or vanity or personal interests were allowed to interfere.

Presented at a meeting of the Rudolph Virchow Medical Society in the City of New York, held on April 4, 1955, at the New York Academy of Medicine.

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As he anxiously watched over the purity of medical science, he was equally concerned about the ethics of medical practice. He deplored the deterioration in physician-patient relationship and held to Naunyn's dictum: "Medicine must be science or it will not be at all." In his eulogy of the great master he said, "The practitioner does not need to be a man of science, but he must have the knowledge of the secure achievements of science, and be able to make use of them." And again he quoted Naunyn: "Where science ends there does not begin art, but crude empiricism." "Those who say that they practice medicine as an art are therefore not yet artists." It sounds like a warning for the present when he then continued, "The scientific aspect of our profession is our strongest hold. If we become weak in this part, then it is only natural that there will be withheld from us the respect which is otherwise given to science," and "Respect and confidence of one's patients is gained best if one attends to them honestly and with devotion but without magic, even if one thus cannot show the utmost degree of sympathy."

Magnus-Levy took this function of a guardian so seriously that we of a younger generation knew him only as the man with the stern face and the uncompromising mind, the earnest speaker and feared critic. Few of us had the privilege to see the warm, modest, deeply emotional and gracious personality which was hidden behind this face. When finally, as he put it, "The crime of 1933 put an ignominius end to a great tradition and blighted a prolific growth," there was no further task left for him in Germany. At the age of seventy-five years, he was obliged to leave the country of his birth and of his labors. He then came to America. His work was well known here and had influenced the development of scientific medicine in this country, either directly or through his American friends, Benedict, DuBois, the Flexners, Fulton, Held, Joslin, E. Liebman, Lusk, and others. He had been honored in 1910 as one of the first guest lecturers of the Harvey Society of the New York Academy of Medicine. In 1940, he was offered a professorship in Professor Fulton's Department at Yale University. He occupied this last public office for five years and then retired to New York where for another decade he followed with interest the development of modern medicine. He was particularly interested in the introduction of isotopes in the study of metabolic problems and noted with satisfaction that the BMR continued to have significant value. He also took great pleasure in the pursuit of historical and literary interests which he had abandoned in his youth.

The data of his life are easily recounted. He was born in Berlin on Sept. 10, 1865, and grew up in a period when Germany was respected as the country of the poets and scholars. The Medical School of Berlin was of world renown, famed for men like Helmholtz, Dubois-Reymond, Waldeyer, Virchow, Traube, and Frerichs. Yet he entered Medical School—as he states in his memoirs which he left to his family—more on the advice of others than out of desire or inclination; possibly he was influenced also by the ravages which diseases had taken in his family. His father, a sister, and a brother had died early of infectious diseases, and his mother suffered from diabetes. His first intention was to study history, and still many years later he considered it a distinct honor to be permitted to meet the great historian Theodor Mommsen. During the first few quarters at Medical School in Berlin, Heidelberg, and Erlangen, he was still doubtful as to whether he should continue. The almost exclusive emphasis of the teaching on structural pathology and on morphology did not satisfy his curiosity. With his historical interest, he may have thought of the words of Jean Fernel, the French scientist of the sixteenth century: "What geography is to history, such is anatomy to medicine—it describes the theatre of the events." It was the events, the functions in the microcosmos of the healthy and sick human body, which attracted him more and more.

In Karl Ludwig, the great physiologist whose lectures he attended in Leipzig (1886-88) he found an inspiring teacher of similar direction, and under Ludwig's influence he decided to apply physiological methods to the clinic. In 1890 he received his M.D. degree in Heidelberg. Immediately he undertook three further years of postgraduate study in physiology and organic chemistry, the former under Nathan Zuntz in Berlin where he became acquainted with the methods of gas analysis and energy exchange, the latter under Fr. Baumann in Freiburg, who at that time was engaged in the chemical analysis of the thyroid extracts. In 1893 he received his Ph.D. Then followed eight years of assistantship (1893-1901) filled with the accumulation of clinical experience and even more with the development of technics for clinical metabolic studies.

During his two years at a municipal hospital in Berlin (UrbanKrankenhaus) under Albert Fränkel, the discoverer of the pneumococcus, and the one year at the City Hospital at Frankfurt-am-Main under Carl von Noorden, famous for his work in nutrition and diabetes, he worked feverishly in the laboratories which he had equipped mostly with his own funds and ac-

cumulated data regarding energy exchange in health, in obesity, in diabetes, and in myxedema. The latter he took up particularly after Friedrich von Müller had suggested that in exophthalmic goiter the metabolism must be increased (1893) and after Leichtenstern and Murray (1894) had inferred from clinical observations that the weight reducing effect of thyroid hormone in obesity might be due to increased energy production. He quickly proved this concept with his new objective method. In 1895, he published the now classical paper "On the Respiratory Metabolism under the Influence of the Thyroid and in Various Pathological Conditions." (In 1942 he was to publish in America a brief paper, "The BMR in the Same Person after an Interval of Fifty Years" in which he demonstrated that in old age the BMR decreases by about 10 per cent.)

The work of 1895 established his reputation immediately and brought him the invitation from Naunyn to join the staff of the Strassburg Clinic. There he concentrated on his now equally classic investigations on diabetic acidosis which culminated in the isolation of beta-oxybutyric acid, and in the demonstration that incomplete fat oxidation and the accumulation of ketone acids, particularly beta-oxybutyric acid, are the cause of the acidosis. Naunyn's school, particularly Hallervorden and Stadelmann, had postulated that diabetic coma was due to acid poisoning. They had shown in animals that intoxication with inorganic acids caused symptoms almost identical with those of diabetic coma. But they had been unable to demonstrate the mechanism of this acid poisoning in the disease, nor had they succeeded in identifying the acids involved. It is characteristic of Magnus-Levy's interests, which even in this period were predominantly clinical, that he felt more pride in the elucidation of the mechanism of diabetic acidosis than of his chemical analytical achievement. The crystallization of the acid nevertheless earned him highest praise from Emil Fischer, the great chemist. In 1899, he became a Privatdozent (instructor) with the thesis "Oxybutyric Acid and its Relation to the Diabetic Coma."

In 1901, he returned to Berlin where he resided until 1940. In 1905 he was appointed a Titular Professor at the University of Berlin. From 1910 to 1922, he was Chief of the Medical Service of a municipal hospital in Berlin (am Friedrichshain) but resigned from this position in order to have more time for research and for his private practice. His friend His, the director of the first Medical University Clinic of the Charité in Berlin, offered him the opportunity to continue his work there in a small laboratory. Here he completed older investigations on multiple myeloma which later (1938) were published as a monograph in the Acta Medica Scandinavia; the new regime had deprived him of the possibility of having his work printed in Germany. The total list of his publications is small, less than fifty, but of each it can be said that it was of highest standard, and even today they are inspiring and most informative. To name only a few: "The Physiology of Metabolism" (1908), "Chemical Problems of Diabetes" (1910), "Acids and Bases in Disease" (1930).

An appraisal of Magnus-Levy would not be complete without an attempt to portray his personal greatness in addition to his accomplishments as a physician and a scientist. Here it seems most fitting to give testimony with his own words. When his family and friends were assembled at his bier for a last farewell, a letter which he had prepared for this hour was read to us. Part of this "letter of thanksgiving" which undoubtedly was meant for a greater audience should be placed here. As earlier in his scientific work he had been the representative of a whole era, so now, speaking for himself, he becomes the speaker for a group of people whose fate he shared.

The letter starts with a quotation from Conrad Ferdinand Mayer's Hutten: "A boat approaches. I travel far. A last word, a word of gratitude." After the expression of thanks to his beloved daughters, his personal friends, to Yale University and Professor Fulton, and to the home where he spent the last years of his life, he continues: "Thanks: to the land of the free which has accorded among countless other exiles, to myself such generous reception, protection and shelter and has restored to all of us peace and dignity.

"to the American medical community which has met me with such human understanding and friendship and has judged my professional services with a degree of benevolence and recognition such as I have never found in wider circles of the old country.

"to the many friends whom I have found here in my advanced years and whose affection has made these years easier and more joyful. Thus in my advanced years has come to me tranquility and ease and an almost steady satisfaction such as I have never known before and had not expected to find in life."

It is now for us to give thanks. Magnus-Levy has reminded us in one of his papers of the Biblical proverb of the fathers: "Thou owest greater thanks to thy teachers than to thy father, for he gave thee only bodily existence, but they gave you spiritual life." Magnus-Levy was such a teacher.

Organization Section

The Annual Banquet

June 4, 1955

The Annual Banquet of the American Diabetes Association was held on Saturday evening, June 4, at the 15th Annual Meeting of the Association in Atlantic City, New Jersey. Henry B. Mulholland, M.D., President, whose Address was published in the July-August issue of DIABETES, was the first speaker. Following his call for rededication to the principles and objectives upon which the Association was founded, he introduced Carl F. Cori, M.D., Professor of Biochemistry, Washington University School of Medicine, St. Louis, Missouri, and Nobel Prize Recipient in Medicine and Physiology, 1948. Dr. Mulholland presented Dr. Cori with the Banting Medal in behalf of the American Diabetes Association.

PRESENTATION OF THE BANTING MEDAL TO DR. CARL F. CORI, BY DR. HENRY B. MULHOLLAND, PRESIDENT, AMERICAN DIABETES ASSOCIATION

It is my honor to present to you a scientist whose research has led to a better understanding of the action of insulin and the fundamentals of carbohydrate metabolism. Born in Czechoslovakia, receiving his early education in Austria and Prague, he came to this country in 1922 and entered the research and teaching field in medicine. He is now Professor of Pharmacology and Biochemistry at Washington University Medical School, St. Louis.

Dr. Cori is a recipient of many honors and awards, including the Willard Gibbs Medal of the American Chemical Society, the Sugar Research Foundation Award, the Lasker Award, the Squibb Award with his wife, Dr. G. T. Cori, and a Nobel Prize in Medicine and Physiology, also with his wife, for their work in fundamental carbohydrate metabolism. He is a member of many scientific organizations and this afternoon he gave the annual Banting Memorial Lecture to the Association.

It is a pleasure to present to you, in behalf of the American Diabetes Association, the Banting Medal which was established by this organization in 1941.

PRESENTATION OF THE BANTING MEDAL TO DR. EUGENE F. DuBOIS, BY DR. ELLIOTT P. JOSLIN, HONORARY PRESIDENT, AMERICAN DIABETES ASSOCIATION

In behalf of the American Diabetes Association, Dr. Elliott P. Joslin, Honorary President, presented the Banting Medal to Dr. Eugene F. DuBois of New York. Dr. DuBois was born in West Brighton, New York, on June 4, 1882. He received the degree of A.B. from Harvard in 1903 and the degree of M.D. from the College of Physicians and Surgeons (Columbia University) in 1906. He held a series of appointments in Cornell University Medical College in New York. He was Professor of Medicine 1930-1940 and Professor of Physiology 1940-1950. He was also Medical Director of the Russell Sage Institute of Pathology 1912-1950. He served in the U. S. Navy in both World Wars and was awarded the Navy Cross. He was Chairman of the Committee on Aviation Medicine of the National Research Council 1940-1945. His interest in diabetes was related to his extensive metabolic research.

REMARKS OF DR. ELLIOTT P. JOSLIN IN PRESENTING THE BANTING MEDAL TO DR. DuBOIS

Dr. Eugene F. DuBois, 73 years old today, whom we of the American Diabetes Association, here assembled, wish to honor tonight is my friend and your friend. He has also been the friend of countless medical students and aspiring investigators, the friend of everyone whose life has been shattered by a deranged metabolism, and while active in the medical corps in two World Wars, the friend of sailors in submarines and aviators in aeroplanes. Dr. DuBois, we salute you! Sir, you have described your life's activities as "trained first in medicine, then diverted into pathology, pathological physiology, physiology, nutrition, private practice, academic medicine, military medicine and finally into the teaching of physiology to medical students." Time does not allow one to repeat the universities, medical schools, hospitals and societies with which you have been connected.

I first knew you because of my association for ten years with Francis G. Benedict, creator of modern calorimeters, who with Atwater built the Atwater and Benedict calorimeter and later carried on in the Nutrition Laboratory of the Carnegie Institution of Washington situated in Boston. Dr. Benedict once told me that he considered you the master technician in the world in the field of metabolism so that I always came to look upon you as the Raphael of your art. You had such a touch of perfection in everything you said or did.

I love to reread the dedication of the three editions of your book *Basal Metabolism in Health and Disease* to—"GRAHAM LUSK, pupil of Voit, pupil of Liebig, pupil of Gay-Lussac, pupil of Berthollet and LaPlace, pupils of Lavoisier." The book was written as you say

"to bring basal metabolism out of the realm of pure physiology into the domain of clinical medicine," and it succeeded.

Imagine the comfort it was to have your seal of approval on our tests with our severest diabetics, some showing such bizarre respiratory quotients as 0.67, 0.68, 0.69 and over 100, which we could not then satisfactorily explain and were glad to have Krogh later interpret as not always indicative of the quantities of carbohydrate, protein and fat burned.

You were the creator of surface area and of the normal standards universally employed today. I recall Henry Christian's metaphor in his tribute to Otto Folin. "As it has been said of the British Empire that the sun never sets upon it, so the sun somewhere always is shining on the laboratory determining something in the blood of patients by a Folin method." And, I will add, so too in some hospital where estimates of basal metabolism are being carried out.

Dr. DuBois' investigations in metabolism covered a multitude of subjects in health and disease. This scope was manifold—surface areas, fever, goiter, typhoid, malaria, erysipelas, cretins, dwarfs and legless men, pernicious anemia, diabetes, cardiac, renal disease, caffeine, the young and the old, the prone and the resting, the mechanism of heat loss and temperature regulation. I have not begun to recount all in the list. These "Arbeits" mentioned, Dr. DuBois, represent only one of your gifts to posterity, but you have left a dual gift with the help of your dear wife in your three children. Particularly we doctors know of your son, who already in medicine has acquired distinction. I am, therefore, asking Professor Arthur B. DuBois to come forward to accept with the love of us all for his father, *un Chevalier, sans peur et sans reproche,* the Banting Medal of the American Diabetes Association.

REMARKS OF DR. EUGENE F. DuBOIS FOLLOWING PRESENTATION OF THE BANTING MEDAL (ABRIDGED)

For many reasons I am deeply appreciative of the presentation of the Banting Medal. This happens to be my birthday and I have never had a better birthday present. After all, diabetes was my first love in research and I feel that it is a great privilege to receive this honor from the American Diabetes Association.

It is a particular honor to receive this medal at the hands of Dr. Elliott Joslin. Like so many others I have been indebted to him for many things for many years. Most important of all is our indebtedness to him for serving as a model whom we can hold up to our medical students.

Recently I was asked to describe the important components of a fine piece of medical work. Naturally, I cited the characteristics of Dr. Joslin's work. These include exact and hard labor to gather the facts, the infusion of the spirit of Christianity, and the permeation of the work with the worker's own individuality. All these are readily recognizable in all of Dr. Joslin's research and in all of his publications. I have followed so closely most of the studies of Joslin with Benedict and have drawn so heavily on their data that I can vouch for the long hours of extremely exact technic and for the care and accuracy of their statistics. I do not know of any program for the treatment of any disease which contains as much of the spirit of Christianity as Dr. Joslin's long campaign to improve the condition of patients with diabetes. As for the infusion of his own individuality, his publications are as characteristic of Joslin as are the paintings of Rembrandt or the musical compositions of Mozart characteristic of their origins. Let us hope that much of his spirit may be copied by the whole school of American medicine.

I cannot convince myself that my own contributions to the subject of diabetes have been important. I merely followed in the paths of Graham Lusk, Frank Benedict, and Elliott Joslin. The great contribution of Graham Lusk was his insistence on the fact that, while it was important to study the intake of food and output of carbohydrate and ketones in the urine, it was even more important to study by direct method what was happening inside the patient during the twenty-four hours. I had the good fortune to apply these principles in the study of the famous patient, Cyril K.* (The data on Cyril K. have been recalculated by many able investigators and each time it seems possible to use the data to support a different theory of diabetes! For example, Graham Lusk used Cyril K. as an example of complete diabetes, but Joslin used these data to show that no diabetic was completely diabetic or hopeless.)

I am particularly happy to have this opportunity of paying tribute to an important phase of the work of Sir Frederick Banting, a phase that has been too much neglected in comparison with the attention given his brilliant work in diabetes. During World War II Sir Frederick Banting was made Chairman of the Associate Committee on Medical Research, and of the Subcommittee on Aviation Medicine of the National Research Council of Canada. Articles about his work in aviation

*Editor: The detailed studies in the case of Cyril K. (H. R. Geyelin and E. F. DuBois, *Journal of the American Medical Association* 66:1532, 1916) yielded important information regarding the metabolic defects in severe diabetes.

medicine have been published by Hipwell and by Harris, but I wish to add my own personal tribute. At that time I happened to be Chairman of the Committee on Aviation Medicine of the United States National Research Council and I saw a great deal of Banting's work. It was of the greatest importance. All of the members of our committee had the highest regard for his wisdom, his energy, his tact, and his devotion to the cause of the Allies.

At the time that Banting was in charge of research in aviation medicine in Canada, the Canadians were leaders in this field and the scientists of the United States and in Great Britain depended upon their data and copied their methods of research. It is significant that Banting displayed the same leadership in this field that he did in the field of diabetes. It shows Banting's versatility and indicates that the discovery of insulin was no mere accident. Had it not been for the unfortunate aviation accident that killed Sir Frederick Banting in the line of duty, we might have had a long line of medical discoveries as a product of his work and knowledge and ingenuity. The work in aviation medicine has been better publicized in the United States than in Canada and we tend to forget that most of it was Canadian in origin. For example, the Canadians were pioneers in studies with the human centrifuge, and the Canadian, Franks, was responsible for the first important work in suits to protect against the effects of gravity. These were later modified and developed by many other investigators. The Canadians also made important contributions in the study of "bends" in aviation. They were leaders in the development of survival kits for aviators forced to descend in cold regions and they gave us some of the earliest scientific studies on clothing. It was they who developed the "clo" as a standard unit of protection.

Some years later when I was assigned to the detail of reporting on the aviation equipment used in the flying fields of England, I noted that many articles of equipment in demand by the pilots were Canadian in origin. The easiest way to tell which articles are most highly regarded by aviators is to find out which articles are most frequently stolen or sought for in exchange of equipment. I suppose the stealing of Canadian and British equipment by our aviators was highly deplorable but these two tests, the "swopping test" and the "swiping test" gave evidence of desirability and were helpful in modifying our American design.

It is my hope that some of the many physiologists who saw Banting's work in aviation medicine will describe in more detail his contributions in this field. They have been sadly neglected.

I am particularly grateful to the American Diabetes Association for giving me this opportunity of paying my small tribute to a neglected aspect of Banting's genius.

PRESENTATION OF THE BANTING MEDAL TO DR. HENRY B. MULHOLLAND, BY DR. RANDALL G. SPRAGUE, PAST PRESIDENT, AMERICAN DIABETES ASSOCIATION

In accordance with custom, it is my privilege as the most recent Past President to speak for the Association in honoring its outgoing President.

Most of us know Dr. Mulholland for his kindliness and friendliness as well as for his great contributions to organized medicine, to medical education, teaching and research and, most important of all this evening, for what he has done for diabetic patients as Councilor and Officer of the American Diabetes Association. He has been President of our Association during a year of development and broadening of its activities. In this capacity he has given us wise and dependable leadership. He has occupied with dignity and ability the position of director of what one might liken to a huge symphony orchestra, the pieces of which are our individual members, our Committees, our Council, our National Office with its capable director and personnel and, indeed, to some extent, the general public. Dr. Mulholland knows the score and has kept all parts of our symphony working in harmony.

Meanwhile, as he has done for many years, he has carried on his work as Professor of Medicine at the University of Virginia. Here, in spite of his heavy outside responsibilities, he has continued active in teaching, administration and the care of patients, particularly diabetic patients.

Dr. Mulholland, your colleagues and friends in the American Diabetes Association are proud of you and grateful to you for your fine unselfish service to the Association. Diabetic patients generally owe you a debt of gratitude. It is a real privilege for me, in behalf of the Association, to present you with the Banting Medal.

PRESENTATION OF CITATION TO HAMILTON RICHARDSON, IN ABSENTIA, BY DR. HENRY B. MULHOLLAND

The American Diabetes Association has on several occasions awarded citations to diabetics who have been outstanding in their accomplishments. Tonight we are particularly fortunate in selecting for such a citation a young man who richly deserves our commendation. A diabetic for years, he has risen to the heights of the great in tennis and is now a member of the United States Davis Cup Team and ranked number three in tennis in this country. As a scholar he has been outstanding, evi-

denced by his election to Phi Beta Kappa, and recently he was the recipient of a Rhodes Scholarship.

It has been my pleasure to meet this young man and to have personally followed him in action on the tennis court. He stands out as an example to other diabetics of the world by his ability to live a normal life and his development of a philosophy of getting along and attaining superior heights, both physical and academic, in spite of his condition.

We regret that he cannot be here himself to receive this citation as he is now in Europe representing this country in important tennis tournaments. It is a pleasure, however, to present this to his mother, Mrs. Roger W. Richardson, who I am sure has played an important part in making him what he is today.

INTRODUCTION OF MR. CHARLES F. KETTERING, RESEARCH CONSULTANT AND DIRECTOR, GENERAL MOTORS CORPORATION, BY DR. HENRY B. MULHOLLAND

This gentleman who has honored us tonight by consenting to address us was born on a farm near Loudonville, Ohio. He had his fundamental education in the graded schools of his district and graduated in 1904 with a degree of electrical engineering and mechanical engineering. As an undergraduate he was elected to Sigma Xi and Tau Beta Pi, honorary organizations. It is fascinating to read his list of contributions to the field of invention which includes the electric cash register, the self-starter, the Delco light farm electrification system, the two-cycle Diesel engine and many other fundamental inventions in the automotive field while heading up the research laboratories of the General Motors Corporation in Dayton, Ohio.

Many physicians will remember that he invented a fever machine which at one time was widely used in the treatment of arthritis. His versatile and active mind has led him into many fields such as photosynthesis and the improvement of soils and agriculture. It is noteworthy that in 1929 due to his generosity and that of Mr. Sloan, the Institute which bears their names was established for cancer research, to which the world is indebted. His honors are many, including the Sullivant Medal, the John Scott Memorial Award, the Gold Key of the American Congress of Physical Therapy and many others. He has been awarded honorary degrees by twenty-five different universities and he is also an Honorary Fellow of the National Academy of Sciences.

We are indeed honored in having him talk to us tonight and I am delighted to present to you Mr. Charles F. Kettering, affectionately and familiarly known to his colleagues as "Boss Ket."

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Herbert Pollack, Chairman
David W. Carter, Jr., Garfield G. Duncan, Robert L. Jackson, Norman H. Jolliffe, Mrs. J. H. Martin (by invitation), William H. Olmsted, Fredrick J. Stare (by invitation), Eugene H. Stevenson (by invitation), Priscilla White, Dwight L. Wilbur

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Joseph T. Beardwood, Jr., George J. Hamwi, Hugh Jeter, Norman H. Jolliffe, Cyril M. MacBryde, Morris Margolin, Helen E. Martin, James M. Moss, O. Charles Olson, Herbert Pollack, Charles Weller, Frederick W. Williams

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REVISION OF *DIABETES GUIDE BOOK FOR THE PHYSICIAN*

Frank N. Allan, Chairman
Garfield G. Duncan, Robert L. Jackson, Frederick W. Williams

SCIENTIFIC EXHIBITS

William R. Kirtley, Chairman
Edward S. Dillon, Marshall I. Hewitt, Howard F. Root, George F. Schmitt, Donald S. Searle, J. Lawn Thompson, Jr.

SCIENTIFIC PROGRAMS

John A. Reed, Chairman

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Garfield G. Duncan, George M. Guest, John E. Howard, Francis D. W. Lukens, Alexander Marble, E. Perry McCullagh, Randall G. Sprague

SCIENTIFIC PUBLICATIONS
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Edgar A. Haunz, Robert L. Jackson, E. Paul Sheridan, Charles R. Shuman, Leon S. Smelo, Kendrick Smith

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E. Perry McCullagh, Chairman
Francis D. W. Lukens, Randall G. Sprague

DELEGATES TO THE NATIONAL HEALTH COUNCIL
Alexander Marble, Herbert Pollack, J. Richard Connelly

SECOND CONGRESS OF THE INTERNATIONAL DIABETES FEDERATION

The Second Congress of the International Diabetes Federation was held in Cambridge, England, July 4-8. At the Opening Ceremony in the Senate House of the University of Cambridge on July 4, addresses of welcome were given by the Vice-Chancellor of the University; the Mayor of Cambridge; the Honorary President of the Congress, Sir Lionel Whitby; the President of the Federation, R. D. Lawrence; and other speakers. Following the Opening Ceremony, Elliott P. Joslin, Honorary President with Charles H. Best, of the International Diabetes Federation, delivered the Ninth Banting Memorial Lecture of the British Diabetic Association. His subject was "Diabetes for the Diabetics."

The Programme of Lectures was opened July 5, by Doctor Best, Toronto, who spoke on "Outstanding Problems in Diabetes: the Present Position of Some of Them." Other members of the American Diabetes Association who presented lectures later that day include Howard F. Root, Boston, "A Report of Progress by the Diabetes Committee of the United Community Services"; and Franklin B. Peck, Sr., Indianapolis, "Diabetes in the Americas."

Lecturers on July 6 included: F. G. Young, Cambridge, "Some Aspects of Experimental Diabetes"; M. Jersild, Copenhagen, "Four Years' Clinical Experience with the Lente Trilogy. Treatment of over 1,000 Patients"; R. G. Paley, Leeds, with R. E. Tunbridge and G. R. Fryers, "Clinical Experiences with the Insulin Zinc Suspensions"; R. E. Haist, Toronto, "Some Effects of Glucose, Insulin and other Agents on the Islets of Langerhans"; M. G. Goldner, Brooklyn, with B. W. Volk, "Effect of Prolonged Growth Hormone Administration on the Pancreatic Alpha Cells in Hypophysectomised Rats"; George E. Anderson, Brooklyn, "Glucagon as a Potentiator and Trigger Mechanism to Insulin Function"; P. de Moor, Antwerp, "The Pathogenesis of Alloxan Diabetes"; J. L. R. Candela, Madrid, with R. R. Candela, J. Rovira and J. Arriba, "Alloxan Hypoglycemia"; John W. Patterson, Cleveland, "Chronic Experimental Diabetes; (Cataracts in Rats)."

On Thursday, July 7, these lecturers spoke: Wilfred Oakley, London, "Lesions of the Feet in Diabetes"; Ewen Downie, Melbourne, "The Conservative Management of Infection and Gangrene of the Lower Extremity"; Franklin B. Peck, Sr., Indianapolis, with Franklin B. Peck, Jr., "Tautologous Diabetic Coma—A Behavior Syndrome"; Henry T. Ricketts, Chicago, "Spontaneous Diabetes in Dogs: an Account of Eight Cases"; R. G. Paley, Leeds, "Pulmonary Tuberculosis in Diabetes Mellitus"; Frank N. Allan, Boston, "Spontaneous Hypoglycemia and Hyperinsulinism"; J. L. R. Candela, Madrid, with R. R. Candela and Y. Valladares, "Plasma Insulin Effects"; J. L. R. Candela, Madrid, with R. R. Candela, J. Rovira and J. Arriba, "Plasma Insulin Effect after Glucose Tolerance Test"; Jakob Mollerstrom, Stockholm, with Arne Sollberger, "Diurnal Rhythm in the Excretion of Citric Acid in Diabetes."

These lecturers presented papers on the final day of the Congress, July 8: Laurance W. Kinsell, Oakland, with Lester Lawrence and Robert D. Weyand, "Hypophysectomy in Patients with Diabetic Vascular Disease.

Clinical and Metabolic Observations"; Henry Dolger, and Robert Joelson, New York, with John J. Bookman, "Some Observations from a New Prenatal Diabetic Clinic's First Two Years' Experience"; Alfred E. Fischer, New York, with Ralph E. Moloshok, "Clinical Features and Management of Infants Born to Diabetic Mothers"; J. P. Hoet, Louvain, with L. Brasseur and R. De Meyer, "Pregnancy during Pre-diabetes: Fetal and Maternal Implications."

Clinical demonstrations were conducted at Addenbrooke's Hospital, Cambridge, on Wednesday afternoon, July 6. Instructional films and films concerned with children's camps were shown Tuesday evening. Among other exhibits at the Congress an exhibition of the different kinds of insulin and syringes in use throughout the world was of particular interest.

Tours and excursions were available each day for members of the families of those attending the sessions. Social events included a garden party held in the grounds of Downing College at which Sir Lionel and Lady Whitby were hosts, and a dance organized by the Ladies' Social Committee under the Chairmanship of Mrs. F. G. Young. A highlight of Congress festivities was a dinner given in the evening of July 6 in the Hall of Trinity College at which Lord and Lady Adrian were present. Lord Adrian is Master of Trinity College.

Henry T. Ricketts, President of the American Diabetes Association, attended the Congress as Medical Delegate, and J. Richard Connelly, Executive Director, served as Lay Delegate.

The Executive Council of the Federation held several meetings during the Congress. A Committee on Postgraduate Education was formed with Professor P. Rambert, Paris, as Chairman. All officers of the Executive Board of the Federation were reelected as follows: President, R. D. Lawrence, M.D., London; Vice Presidents, J. P. Hoet, M.D., Louvain, M. Paz, Paris, Howard F. Root, M.D., Boston; Secretary-Treasurer, F. Gerritzen, M.D., The Hague; P. Duys, The Hague, will continue as Executive Secretary. In addition these Vice Presidents were newly elected: Ing. Mario Coppetti, Montevideo; M. Silvestri-Lapenna, M.D., Rome; Viggo Steenberg, Copenhagen.

FOURTH POSTGRADUATE COURSE

The Fourth Postgraduate Course in Diabetes and Basic Metabolic Problems will be held at The Statler Hilton hotel in Dallas, Texas, Jan. 25-27, 1956. It will be conducted by the American Diabetes Association under the direction of Edwin L. Rippy, M.D., of Dallas, an Association Councilor and Chairman of the Committee on Policies.

The main topics of the course will be clinical diabetes and complications of diabetes. Sessions will be held each morning and afternoon of the three days, with round table luncheons scheduled for every day. A social hour and dinner have been planned for January 25, and a social hour for January 26. On the 27th at 8 p.m., a Lay Society Meeting will be held by the Dallas Diabetes Association.

A series of five different one-hour lectures, demonstrations and clinics will be held concurrently on January 26, entitled "Experimental Background of Present Knowledge of Diabetes," "Urine and Blood Tests in Diabetes," "Treatment of Diabetic Ketosis," "Calculating the Diabetic Diet," and "Renal Disorders and Diabetes." Registrants may designate which discussion they wish to attend. On the concluding afternoon five informal seminars on "Degenerative Vascular Complications in Diabetes" will also be held concurrently.

The fee for the Course is $40 for members of the Association and $75 for nonmembers. An application form attached to the Program of the meeting is being mailed to all members of the Association. The registration form should be filled out and mailed, with the fee, to the National Office as soon as possible.

Registrations will be accepted in the order received, and will be officially confirmed. Graduate students, fellows, residents, interns and medical students on full-time study in medicine and allied sciences in the schools and hospitals in the area of Dallas will be admitted without charge to the scientific sessions upon presentation of a letter requesting their admission from their Dean, or the head of their department or service.

SIXTEENTH ANNUAL MEETING

The American Diabetes Association will hold its Sixteenth Annual Meeting in Chicago, June 9-10, 1956, prior to the Annual Session of the American Medical Association, June 11-15. As previously announced, The Drake will serve as headquarters hotel and a number of guest rooms will be available. An announcement of the meeting, together with a hotel reservation card, is being sent to all members of the Association. Members are urged to make their reservations promptly. Please note that the hotel information cards which were mailed in the spring of the year were for survey purposes only. It is essential that members fill out and send directly to The Drake the reservation card which accompanies the announcement. Additional reservation cards may be secured by writing to the National Office.

FOURTH STUDENT-INTERN ESSAY CONTEST

The fourth in a series of Student-Intern Essay Contests is being sponsored by the American Diabetes Association. A prize of $250 will be given to the author or authors of the best paper reporting original laboratory research or clinical study. The prize money is being given by the St. Louis Diabetes Association. An additional prize of $50 will be awarded for the best review article or case report.

Any subject relating to diabetes and basic metabolic problems may be selected. The contest is open to medical students or physicians within two years of graduation. All manuscripts should be submitted to the Editorial Office of DIABETES: *The Journal of the American Diabetes Association,* 1 East 45th Street, New York 17, New York.

NEW MEMBERS

The following Active Members were elected as of Sept. 1, 1955:

Alabama	
Berry, Keehn W., Jr.	Birmingham
California	
Steinbach, Owen K.	Fresno
Colorado	
Ackerly, Roscoe H.	Pueblo
Bosworth, Robert G., Jr.	Denver
Georgia	
Davidson, John K., III	Columbus
DeVaughn, Nathan M.	Augusta
Kansas	
Matassarin, Benjamin M.	Wichita
Kentucky	
Moore, Frank H.	Bowling Green
Massachusetts	
Maloney, John M.	Springfield
Minnesota	
Beddow, Ralph M.	Rochester
Klakeg, Clayton H.	Rochester
Missouri	
Falk, O. P. J.	St. Louis
New York	
Gerstenhaber, Adolf	Brooklyn
Golden, Boris	Niagara Falls
LaTona, Joseph H.	Niagara Falls
Levokove, Emanuel	Far Rockaway
Manong, Stephen T.	Niagara Falls
Markham, Mark J.	New York
Ohio	
Polot, David M.	Cleveland
Werk, Emile E., Jr.	Cincinnati
Texas	
Cannon, George M.	Brownsville
Thomason, Mary Elizabeth C.	Corpus Christi
Utah	
Gross, George D.	Salt Lake City

OTHER COUNTRIES

Canada	
Brown, Charles B.	Toronto
Dickson, R. R. K.	St. Catharines
Judd, A. Barry	Winnipeg
Greece	
Alivisatos, John G.	Athens

The following Associate Members were elected as of Sept. 1, 1955:

District of Columbia	
Gay, Mrs. Marjorie F.	Washington
Illinois	
Reinhold, Miss Elaine R.	Chicago

News of Affiliate Associations

The DALLAS DIABETES ASSOCIATION will hold a meeting September 28, at which Max Miller, M.D., will speak on "Fructose." At the election meeting on December 6, I. Arthur Mirsky, M.D., will speak on "The Role of Insulinase in Diabetes."

The DIABETES ASSOCIATION OF THE DISTRICT OF COLUMBIA has elected the following officers: Samuel D. Loube, M.D., President; James M. Moss, M.D., Vice-President; Louis K. Alpert, M.D., Secretary-Treasurer; Samuel D. Loube, M.D., Chairman, Committee on Detection and Education. The Clinical Society of the Association elected these officers to serve during 1955-1956: James M. Moss, M.D., President; Aaron G. Saidman, M.D., Vice-President and President-elect; DeWitt E. DeLawter, M.D., Secretary-Treasurer.

The NEW YORK DIABETES ASSOCIATION will sponsor a "Symposium on the Pituitary-Adrenal System and Diabetes Mellitus" on Thursday, Oct. 27, 1955, in the Audi-

torium of the Memorial Center for Cancer and Allied Diseases, 410 East 68th Street, New York City. Authorities in their respective fields will discuss experimental steroid and pituitary diabetes as well as clinical observations of disturbances in the pituitary-adrenal axis, their relation to diabetes and their management.

The morning session of the day-long program will begin at 9:30 a.m. Both morning and afternoon sessions are open to interested physicians, medical students and other professional personnel. Advance registration must be made and may be requested from the New York Diabetes Association, Inc., at 270 Park Avenue, New York 17. There is no registration fee.

Henry E. Marks, M.D., President, New York Diabetes Association, will preside at the Morning Session. The following papers will be presented: "Current Concepts of the Action of Insulin," Carl F. Cori, M.D.; "Metabolism of C^{14} Labeled Glucose in Diabetes," Nome Baker, Ph. D.; Discussion, Robert Steele, Ph. D.; "Experimental Steroid Diabetes," Dwight J. Ingle, Ph. D.; Discussion, Joseph W. Jailer, Ph. D., M.D.; "Experimental Pituitary Diabetes," Richard C. de Bodo, M.D.; Discussion, Abraham White, Ph.D.; "In Vitro Observations of Endocrine Relationships in Carbohydrate Metabolism," M. E. Krahl, Ph. D.; "The Role of Insulin and Contra-Insulin Hormones in Metabolism of the Liver," Rachmiel Levine, M.D.; Discussion of two previous papers, DeWitt Stetten, Jr., M.D.

George E. Anderson, M.D., Chairman, Clinical Society, New York Diabetes Association, will preside at the Afternoon Session, when the following papers will be delivered: "The Diabetogenic Action of the Pituitary—Clinical Observations," E. Perry McCullagh, M.D.; Discussion, Olof H. Pearson, M.D.; "Adrenal Hypofunction and Adrenalectomy in Human Diabetes," Irving Graef, M.D.; Discussion, Harold Rifkin, M.D., and Abbie I. Knowlton, M.D.

News Notes

POSTGRADUATE COURSE IN DIABETES

A Postgraduate Course in "Diabetes Mellitus and Endocrinology in Relation to General Medicine" will be given by Harvard Medical School Oct. 10-12, 1955, at the New England Deaconess Hospital under the direction of Howard F. Root, M.D., and associates.

The course will consist of clinical demonstrations and lectures presenting the fundamental physiology, pathology, chemistry, and diagnosis and treatment of diabetes and related endocrine disorders. Chairmen for the course will be Dr. Root, Alexander Marble, M.D., and Leo P. Krall, M.D.

Lecturers and their subjects, listed in order of presentation, will be as follows: Dr. Root, "Clinical Aspects"; Albert Renold, M.D., "Physiology of Diabetes"; Elliott P. Joslin, M.D., "Diabetes Today and Tomorrow"; Dr. Marble, "Diagnosis: Problems and Methods"; Allen P. Joslin, M.D., "Treatment, Early Care"; Dr. Marble, "Insulins"; Samuel Hicks, M.D., "Pathology"; Dr. Krall, "Case Findings"; Jorn Ditzel, M.D., "Studies of Capillaries"; Robert Bradley, M.D., "Diet—Pre- and Post-operative, Peptic ulcer, etc."; Dr. Krall, "Insulin Reactions—Placetone Test"; Frank Wheelock, M.D., "Surgery and Lesions of Feet—Diagnosis"; Theodore Pratt, M.D., Clifford Franseen, M.D., Leland McKittrick, M.D., and John McKittrick, M.D., "Surgery and Lesions of Feet—Examinations"; Dr. Elliott P. Joslin, "Brittle Diabetes"; Dr. Root, "Class Teaching"; William Beetham, M.D., "Eyes"; Dr. Marble, " 'Diabetes' Review"; Luke Gillespie, M.D., Lloyd Sexton, M.D., and Priscilla White, M.D., "Pregnancy—Delivery and The New Born"; Dr. Marble, "Neuropathy"; Dr. White, "Childhood"; Dr. Bradley, "Liver"; Dr. Marble, "Questions and Answers"; Dr. Root, "Clinical Presentations"; Dr. Bradley and Dr. Krall, "Coronary Disease"; Dr. Root, "Insulin Resistance"; Dr. Bradley, "Endocrine Relationships—Thyroid"; Dr. Root, "Endocrine Relationships—Pituitary"; Dr. Marble, "Endocrine Relationships—Pheochromocytoma"; Dr. Bradley, "Dietary Problems"; Dr. Marble, "Island Cell Adenomata"; Dr. Root, "Acidosis and Coma"; Dr. Marble, "Insulin Allergy and Atrophies"; Dr. Root, "Triopathy and Prevention of Complications."

PERSONALS

Members of the American Diabetes Association who will take part in Postgraduate Courses offered by the American College of Physicians include: FRANK L. ENGEL, M.D., Durham, North Carolina, "Physiological Basis of Internal Medicine," Duke University School of Medicine, Oct. 10-14; EDGAR S. GORDON, M.D., Madison, Wisconsin, "Neurological Aspects of Internal Medicine," University of Wisconsin Medical School, Oct. 10-14; JERE M. BAUER, M.D., JEROME W. CONN, M.D., STEFAN S. FAJANS, M.D., and HOLBROOKE S.

SELTZER, M.D., Ann Arbor, Michigan, "Recent Advances in Internal Medicine," University of Michigan Medical School and University Hospital, Oct. 17-22; I. ARTHUR MIRSKY, M.D., Pittsburgh, Pennsylvania, "Recent Developments in Psychiatry for the Internist," The Menninger School of Psychiatry, The Menninger Foundation, Topeka State Hospital, Winter VA Hospital and University of Kansas School of Medicine, Oct. 24-28; ALFRED W. HARRIS, M.D., W. GRADY REDDICK, M.D., and PAUL J. THOMAS, M.D., of Dallas, Texas, "Recent Advances in Cardiovascular Disease," Southwestern Medical School of the University of Texas, Jan. 16-20, 1956.

GRACE GOLDSMITH, M.D., New Orleans, will be discussant of "Effects of Limited Tocopherol Intake in Human Males," at "The Symposium on the Role of Some of the Newer Vitamins in Human Metabolism and Nutrition," to be held at the Vanderbilt University School of Medicine, Nashville, Tennessee, Oct. 20-21. The Symposium is made possible by a grant from The National Vitamin Foundation. DR. GOLDSMITH was a member of the subcommittee of the American Public Health Association's Committee on Administrative Practice which has recently produced a book entitled *Nutrition Practices: A Guide for Public Health Administrators,* describing the role of nutrition in modern public health practice.

C. N. H. LONG, M.D., Chairman of the Physiology Department, Yale University School of Medicine, has been appointed Chairman of a special committee on Medical Research to appraise financial support of medical research by the U. S. Department of Health, Education and Welfare.

The appointment was announced by the National Science Foundation along with the Department of Health, Education and Welfare. Federal support of nonfederal institutions as well as the rate of growth of intramural research will be investigated by the Committee. There will also be a review of the proper balance of effort between fundamental research and that directed at specific problems in prevention, diagnosis and treatment of various diseases.

DANIEL W. HAYES, M.D., Clinical Instructor of Medicine, Louisiana State University School of Medicine, New Orleans, will speak on "Common Problems in the Management of Diabetes" on October 1 at the combined meeting of the Third District Medical Society and the Iberia Paris Medical Society at Lafayette, Louisiana.

HERBERT POLLACK, M.D., Associate Professor of Clinical Medicine, New York University College of Medicine, will speak on "The Altered Prognosis in Diabetes Mellitus" on October 21 at the 64th Annual Meeting of the Association of Life Insurance Medical Directors of America to be held in New York City Oct. 19-21. DR. POLLACK will also be Chairman of a panel and discussion on "Body Weight and Heart Disease" at the American Heart Association's 31st Annual Meeting and 28th Scientific Sessions, to be held in New Orleans, Louisiana, Oct. 22-28. MARTIN G. GOLDNER, M.D., Brooklyn, will act as moderator.

MICHAEL G. WOHL, M.D., Philadelphia, will be Conference Co-Chairman of a "Conference on Nutritional and Metabolic Considerations in Disease" to be held November 9 at the College of Physicians in Philadelphia. The Conference will be presented by The Commission on Nutrition of The Medical Society of the State of Pennsylvania, The Philadelphia County Medical Society and The National Vitamin Foundation. Other members of the American Diabetes Association who will take part in the Conference include NORMAN JOLLIFFE, M.D., New York, "Diagnosis and Treatment of Nutritional Disturbances," with GARFIELD G. DUNCAN, M.D., Philadelphia, as one of the discussants. CAMPBELL MOSES, M.D., Pittsburgh, will discuss a paper entitled "Nutritional Aspects of Cardiovascular Disease (Hypertension and Coronary Artery Disease)."

OBITUARY

BENJAMIN F. SMITH, M.D., was born Sept. 10, 1887, in Bentonville, Arkansas, and died in Houston, Texas, on Nov. 17, 1954, at the age of 67. He received his medical degree from the University of Texas in 1912, and interned at St. Joseph's Infirmary, 1912-13. He was on the staff of St. Joseph's Infirmary, Hermann Hospital and Jefferson Davis Hospital. From 1915 to 1917, Dr. Smith was in charge of the X-ray laboratories at St. Mary's Infirmary, Galveston, Texas. He became instructor in gynecology and obstetrics at the University of Texas in 1917, and later taught electrocardiography at Baylor Medical College. In World War I he served from 1917 to 1919 as Captain in the Medical Corps. In addition to membership in the American Diabetes Association, which he joined in 1941, Dr. Smith was a member of the Texas Club of Internists and the American Heart Association. His publications include a book on diabetes, and a manual of electrography.